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Original Articles by

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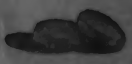
SURGICAL MANAGEMENT OF CARDIOVASCULAR DISEASE

Transcription of a Panel Meeting

LUDWIG W. EICHNA
CLARENCE DENNIS
ANDRE COURNAND
FRANK GLENN
F. JOHN LEWIS



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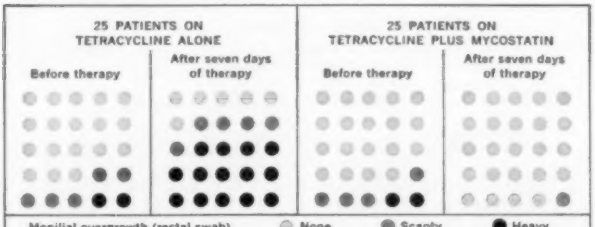

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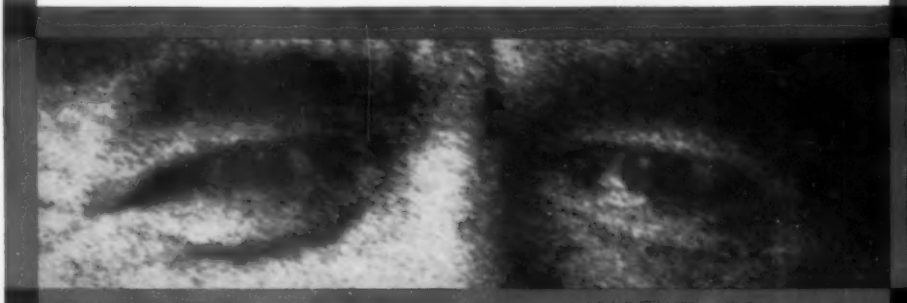

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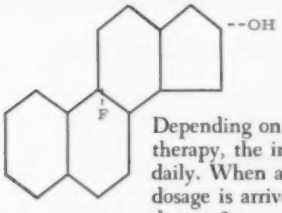

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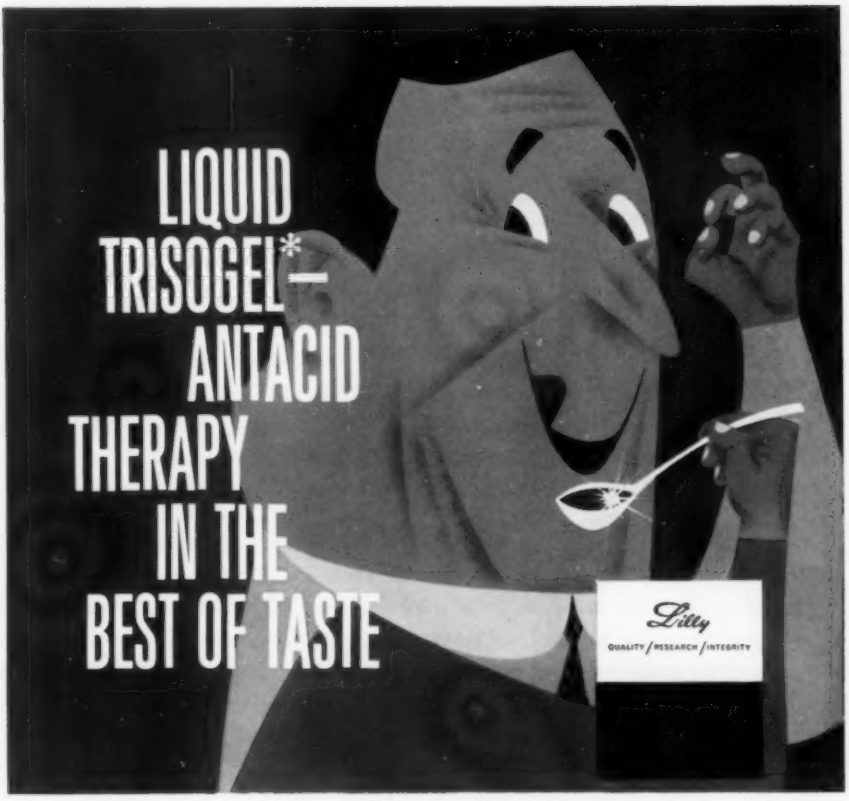

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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RENAL TUBULAR DYSFUNCTION IN CONGESTIVE HEART FAILURE*†

LOUIS LEITER

Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; Chief, Medical Division, Montefiore Hospital, New York

HEART failure involves disturbances in a multiplicity of mechanisms—energetic, mechanical, hemodynamic, tissue metabolic, osmotic, nervous, hormonal, psychologic. The phenomena of congestion and edema are merely the gross manifestations of the imbalance resulting from myocardial failure and the various adaptive mechanisms utilized by the body in its attempt to maintain the circulation. Since an adequate circulation depends considerably on volume, the regulation of the interrelated fluid volumes in the body is of paramount importance[1]. In this regulation the kidney normally plays a key role because it represents the major outflow mechanism. In the abnormal states of fluid retention, as in heart failure, the kidney effects volume control by re-

* Presented at the Postgraduate Week on *Research Contributions to Clinical Practice*, of The New York Academy of Medicine, October 10, 1957.

Much of the research referred to in this paper has been carried out over the years by Doctors R. E. Weston, J. Grossman, and a number of Research Fellows including, more recently, Doctors D. Gibbons, S. Kass, A. Essig, R. Rosenblum and M. Isaacs.

This work has been supported by grants from the National Heart Institute, The National Institute of Arthritis and Metabolic Diseases, The American Heart Association, Eli Lilly and Company, Searle and Company, Sandoz Pharmaceuticals, and Lederle Laboratories.

† From the Medical Division, Montefiore Hospital, New York.

sponding in an exaggerated manner to the various influences, intrarenal and extrarenal, to which it is ordinarily subject. If the results are somewhat surprising or even paradoxical when compared to the elegant adjustments of kidney function in the normal state, this is not really the fault of the kidneys which are only the obedient servants of the integrated body. As effectors, they cannot help but respond to the misinterpretations of receptors, wherever they are. In heart failure, many things go wrong outside the kidneys which are reflected in abnormal communications to the kidneys. When we speak, therefore, of "renal tubular dysfunction in congestive heart failure", we are referring to the entire gamut of reactions of the renal tubules in this condition. In the advanced stages of heart failure, when the heart muscle itself can no longer be influenced directly by drugs and metabolic rest, renal tubular dysfunction and its responsiveness to therapeutic measures become crucial in the clinical situation. At this point, renal tubular behavior virtually determines the course of heart failure and the patient's welfare depends on our ability to influence tubular functions. Some understanding of the mechanisms underlying these tubular activities has been acquired through patient research by many workers. This knowledge, as you will see, has been continuously and successfully applied in the treatment of congestive heart failure.

The renal dysfunction characteristic of heart failure, namely, reduced glomerular filtration rate and renal plasma flow associated with normal tubular excretory and reabsorptive functions, is found in both low and high output types of congestive failure[2,3] as well as in states of shock and dehydration. It may be the most sensitive criterion of an inadequate circulation and, with the exception of the early reversible stages of cor pulmonale precipitated by acute respiratory infections[4], this renal dysfunctional pattern, particularly the low glomerular filtration rate, usually persists to some degree even after cardiac compensation and mobilization of edema. In established heart failure, in the absence of organic renal disease, the demonstration of significant glomerulo-tubular imbalance (defined as normal tubular function, including reabsorption of salt, in the presence of subnormal glomerular filtrate load), has been a productive factor in physiologic and therapeutic research in the past ten years. While this concept has emphasized intrarenal dynamics, it has not excluded but, on the contrary, helped to clarify the role of extrarenal factors, e.g., hormones (aldos-

terone, ADH) and metabolic states, acting upon various segments of the renal tubule.

It is unnecessary to point out to this audience that the reabsorptive function of the renal tubule for sodium, chloride and water, in relation to maintenance of extracellular fluid volume, is closely connected with the ion-exchange mechanism for control of acid-base balance and urinary pH in the distal tubule. It is impossible, therefore, to deal with sodium retention or excretion without considering potassium, hydrogen ion and ammonium excretion. The practical consequences of this relationship in the electrolyte disturbances of heart failure, and its treatment by digitalis and powerful diuretic drugs, are well known to you. They too represent a significant contribution of clinical research to the modern treatment of cardiac edema.

Glomerulo-tubular imbalance, as already defined, has a number of interesting sequels. In the first place, it makes possible the oliguria and high concentration of the urine in heart failure, as well as the reversal of diurnal rhythm in the excretion of water and electrolytes[5, 6]. With the smaller glomerular filtrate, more water can be reabsorbed and the solutes more concentrated, even though sodium chloride may be largely removed by reabsorption. Urea partially replaces it osmotically in the final urine.

Secondly, the reduced glomerular filtration rate (GFR) prevents even the patient in moderate congestive failure from achieving the level of maximal diuresis attained by a normal subject after intravenous water loading[7]. If the percentage of filtered water reabsorbed by the proximal tubule remains normal or is increased, then the flow of fluid reaching the distal tubule must inevitably be reduced. This reduced amount of fluid is further diminished by reabsorption of solute-free water beyond the site of ADH action—collecting tubule? In fact, in severe heart failure with very low glomerular filtration rate and, presumably, sustained production of ADH, water diuresis not only does not occur but congestive failure is aggravated by the retained fluid and paradoxical oliguria may result[7].

Third, the glomerulo-tubular imbalance is the basis for an interesting phenomenon that occurs when a mercurial diuretic is given to a hydrated subject whose urine flow is kept down by continuous infusion of a physiologic dose of Pitressin[8]. This experimental design has been used in an attempt to localize the site of action of mercurials in

the renal tubule, that of Pitressin or endogenous ADH being accepted as the distal tubule. If the mercurial exerts its major action distally, as some have claimed, Pitressin should facilitate a high electrolyte concentration during mercurial inhibition of reabsorption. Actually, the urine originally highly concentrated under Pitressin becomes diluted as though by an iso-osmotic filtrate whose reabsorption, proximally, is inhibited by the mercurial. The urine volume is increased by the amount escaping distal tubular reabsorption under maximal Pitressin activity. The electrolyte concentration rapidly falls, but never quite attaining isotonicity because the kidney is adding an isotonic fluid to a hypertonic one, though the volume of the former is very large relative to the latter.

However, comparison of the composition of the urine just prior to and following mercurial diuresis, and calculation of the sodium content of the fluid not absorbed, or rejected, by the tubule under the influence of mercury revealed two *hypertonic* phases of the tubular rejectate[8, 9]. One occurred at the beginning of diuresis and the other after maximal diuresis, during the waning phase. This speaks for an increase in water reabsorption per unit of sodium, or a higher free water clearance (water reabsorbed without solute) early in mercurial diuresis and, later, during the waning phase. The first increase in water reabsorption can be explained by the fact that under Pitressin the distal final reabsorbing segment is not receiving the amount of water it can absorb, free of solute, before reaching a maximal concentration gradient for the level of ADH activity. The difference between submaximal and maximal absorption of water is actually small, less than 0.5 ml. per minute in normal subjects and somewhat more in cardiacs because of lower glomerular filtration. The second increase in water reabsorption, occurring during the waning phase of mercurial diuresis, suggests that a mechanism is stimulated by the diuretic contraction of extracellular fluid which activates the renal tubule to conserve water and, probably, sodium and thus terminate diuresis. That sodium conservation must occur is indicated by the finding of other investigators of highest aldosterone levels in the urine immediately following mercurial diuresis in normal subjects[10]. In cardiac failure with reduced glomerular filtration rate and normal tubular function, yet not severe enough failure to prevent some excretion of added salt and thus allow a hypertonic urine to form, the effect of combined Pitressin-

mercurial diuresis on the free water clearance and tubular rejectate concentration should be greater than the normal response. This has been demonstrated[9].

It is of interest that in these cardiac patients in mild congestive failure, who were able to tolerate 9 grams of added salt in their diet, this adjustment was accompanied by a significant increase in glomerular filtration rate, something not detected in normal subjects. It is tempting to relate the ability to excrete the extra salt to the increased filtration. Furthermore, the increased osmolality of the pre-diuretic urine in the Pitressin-mercurial experiment in the cardiac, when compared with the normal subject, was associated with changes in the relative sodium and potassium concentrations suggesting, first, that the increase in urinary sodium concentration was not merely the result of pure water reabsorption and, secondly, that distal tubular ion-exchange was involved because of the simultaneous fall in potassium concentration[11]. These are only preliminary studies and will require extension.

These studies of kidney function may also help to explain the differences in the course of mercurial diuresis between non-edematous and cardiac edematous subjects. The latter have much more of a cushion of available extracellular fluid and their circulatory efficiency may actually be improved by initial mobilization of edema. Certain practical aids have been developed as a result of these studies, in dealing with refractory cardiac edema—e.g., aminophylline administration, and elevation and elastic bandaging of the edematous legs of the recumbent patient on the day of the mercurial injection, with a resulting prolonged and much larger diuresis[12]. The precaution must be observed of waiting for definite diuresis to be well under way before carrying out the auxiliary procedure.

The glomerulo-tubular imbalance of heart failure has, as we have seen, certain tubular dysfunctions as important consequences of the purely intrarenal situation. However, the kidneys also are under hemodynamic and hormonal control to permit them to respond to changes in extracellular fluid volume regardless of direction of change in serum sodium concentration to which the intracranial osmoreceptors are so sensitive. The typical normal response to expansion of body fluid volume induced by injections of Pitressin-tannate in oil in subjects on low sodium and high fluid intake, is a sodium and chloride diuresis at the time of the marked dilution hyponatremia[13]. Although a marked

reduction of urinary aldosterone has been observed at this period[10], there is also a significant increase in glomerular filtration rate and renal plasma flow in the normal subjects which could account for the increased sodium excretion. Sodium diuresis has also been produced in a variety of more acute experiments by infusion of hypotonic solutions into recumbent subjects. Here, expansion of intracranial volume may play a role[14].

The situation in patients with congestive heart failure is entirely different. In them, Pitressin expansion of body fluid volumes with electrolyte dilution leads to no change in the very low sodium excretion, no increase in glomerular filtration rate, but usually to aggravation of the signs of congestive failure[15]. From these and other types of experiments it would seem that the kidney can regulate extracellular fluid volume in response to some message from the circulation and its controllers in the normal organism. However, in heart failure the kidney reacts as though the arterial system were not adequately filled and adapts by increased tubular reabsorption of salt and water[16]. This response is reminiscent of the acute and transitory reactions which occur in normal subjects under postural changes (quiet standing), exercise, positive pressure breathing and obstruction of large veins[1]. Here, too, the renal functional changes strongly suggest an adaptation to circulatory stress or underfilling of the arterial system. Similar experiments in patients with heart failure have shown markedly exaggerated responses including decreases in glomerular filtration rate[17]. It is of interest that the transplanted, therefore denervated, human kidney has manifested normal responses to the various circulatory experiments just described[18]. Furthermore, given a maintenance dose of adrenal 11-oxy steroids, the adrenalectomized or Addisonian patient also reacts essentially normally to experimental changes in circulatory volume[19]. Under considerable dispute, still, are the effects of venous compression in the neck on urinary sodium excretion, as evidence of intracranial volume regulators acting somehow on the renal tubules[20-22].

One of the inevitable consequences of the tubular dysfunction in heart failure is increased potassium excretion. This is related partly to the increased sodium reabsorption by ion exchange in the distal tubule, particularly when sodium conservation is stimulated by low sodium diets. The administration of ammonium chloride or cation exchange resins also leads to increased excretion of potassium, with chloride,

because of the unavailability of sufficient sodium in the distal tubular fluid. In the more severe stages of congestive failure many factors, as already described, including the influence of aldosterone, conspire to promote more complete sodium reabsorption by the tubule. In this situation, mercurials and, especially, carbonic anhydrase inhibitors (Diamox) will tend to produce urinary loss of potassium rather than sodium. The result of repeated and prolonged potassium loss coupled with the tendency to poor intake, is depletion of total body potassium. This, in turn, carries with it a host of symptoms, often non-specific and hard to recognize, as well as greater sensitivity to digitalis toxicity and, therefore, difficulties in adequate digitalization[23]. A vicious cycle is easily created which can be interrupted only by adequate administration of potassium.

The ability to produce and excrete ammonia is an important renal tubular function, particularly in view of the widespread use of acid-forming salts or resins as an adjunct to mercurial diuresis. Our group has shown that the kidney in congestive heart failure is not up to par in ammonia-producing ability[24]. This leads to a more prolonged and more severe acidosis ("chloride type") in the cardiac patient. The reason for this tubular defect is still unclear and much more work must be done with improved methods. Preliminary studies have shown that acute increases in renal blood flow and glomerular filtration rate produced by Apresoline in cardiac patients, have little or no influence on urinary ammonia excretion. Other approaches to this problem will be explored, including elevation of the glutamine level in the blood.

From the preceding discussion it is evident that research into some of the mechanisms underlying renal tubular dysfunction in heart failure has led to significant practical applications in the care of difficult cardiac problems. As a matter of fact, the entire question of refractoriness or resistance of severe cardiac edema to mercurials is bound up in the responsiveness of the renal tubule to the various influences that act upon it[12]. Therefore, it becomes of practical importance to know how a low glomerular filtration, severe sodium restriction or depletion, changes in circulating volume, metabolic acidosis or alkalosis, antidiuretic hormone and aldosterone activity, and potassium depletion, can modify tubular function in heart failure. From this knowledge stem such useful therapeutic measures as the potentiation of mercurial diuresis by aminophyllin given at the right time, by ammonium chloride

properly supported by potassium, by elevation and elastic bandaging of the legs to prolong mercurial diuresis in resistant cases; the optimal time sequence in the combination of Diamox and mercurial diuresis, to take advantage of the augmenting effect of hyperchloremic acidosis and urinary acidity on mercurial action; the prevention and control of digitalis toxicity by adequate potassium intake; the adjustment of dietary salt intake to the degree of failure and amount of exercise, rather than rigid uniform restriction for all edematous patients. All of these therapeutic advances exemplify research contributions to clinical practice.

Many problems remain to be solved and progress is at times painfully slow. However, experience has shown that the fundamental investigations of disturbed physiologic mechanisms in disease, while more difficult than ad hoc clinical studies, are in the long run more productive and rewarding to all concerned.

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THE KIDNEY AND POTASSIUM*

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THIS evening I would like to discuss three interrelated problems that involve the kidney and the potassium ion. First, the manner in which the kidney regulates potassium excretion; secondly, the effects of severe potassium depletion on various renal functions; and third, the problems that are posed by the entity that has been called "potassium losing nephritis".

Potassium balance is of course maintained by renal mechanisms which respond to variations in dietary intake and in extra-renal losses. Since the amount of potassium that is normally excreted can be accounted for by the reabsorption of all but about 10 per cent of the potassium in the glomerular filtrate, it was formerly thought that the renal mechanism was one of filtration and reabsorption. However, in recent years it has been shown that under certain circumstances the amount of potassium excreted is greater than the amount filtered at the glomerulus. Hence we are dealing with a triple mechanism—filtration, reabsorption and tubular secretion.

It would be nice if we were able to measure reabsorption and secretion separately but this obviously is not possible in the intact animal. Many workers have suggested that the simplest explanation of all the data is that reabsorption is virtually complete and that urinary excretion is regulated by the secretory mechanism[1, 2]. The following generalizations support this concept. First, in acute experiments the amount of potassium excreted can vary independently of the amount filtered[3]. Second, unequivocal secretion can be demonstrated under conditions which are usually associated with an increase in potassium output. These include dehydration, increased potassium intake, and acute alkalosis[4, 5]. Third, in certain pathological states characterized by an excessive renal loss of potassium there is clear evidence of secretion as shown by clear-

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ance ratios[6, 7]. Fourth, when drugs such as mercurial diuretics and carbonic anhydrase inhibitors are examined under a wide range of experimental conditions, the effects on potassium excretion seem best explained by the concept of continuous secretion, even though the actual amount of potassium excretion may be less than the amount filtered[8]. And, finally, most of the changes in potassium excretion that are produced by disturbances in acid-base balance can readily be interpreted on the basis of the secretory mechanism[2]. Studies with radioactive potassium have shown a rapid equilibration between the potassium of the kidney cells and that of the voided urine, a finding that is quite compatible with this concept of the secretory mechanism[9]. However, one line of evidence must be cited as not being consistent, and that is the micropuncture studies. Although earlier reports from Dr. Phyllis Bott suggested complete reabsorption, her more recent work is less conclusive; evaluation of the renal mechanisms by this technique must await further studies.

Reabsorption has not been adequately studied at the cellular level and little can be said about this mechanism. Secretion has been described as an exchange reaction by which sodium from the tubular urine is exchanged for potassium from the cell. In addition, it has been postulated that hydrogen and potassium ions compete to exchange with sodium. There are a number of independent variables: 1) the cellular concentration of potassium, 2) the sodium concentration in the tubular urine, 3) the concentration of hydrogen ion, 4) the capacity of the exchange mechanism itself, which may well be regulated by adrenal steroids or modified by various drugs, and 5) the concentration of anions in the urine which necessarily must influence cationic concentration. Since each of these factors may vary independently, it should not be surprising if our understanding is incomplete and that some of our concepts may even appear contradictory.

Let us now consider how this secretory mechanism might be influenced by variations in the local ionic concentrations. On the basis of the law of mass action, one would predict that a high concentration of sodium in the tubular urine would facilitate potassium secretion, a low concentration would depress it. A number of observations have confirmed the validity of this prediction. Perhaps the most common situation is the accentuation of potassium deficits seen with the excessive administration of sodium chloride to patients maintained on parenteral

fluids. But somewhat more dramatic is the marked effect that the sodium balance has on the action of the adrenal steroids. Many years ago, Ferrebee and his associates[10] showed that desoxycorticosterone increases the excretion of potassium to the point of severe depletion, and more recently several groups have shown that this does not occur when sodium is restricted in the diet, and hence when its concentration in the urine is very low[11]. Occasionally the opportunity arises to use this phenomenon as a therapeutic measure. I am indebted to Dr. J. E. Howard for the data on a patient who suffered from a severe potassium deficit which persisted despite an almost complete adrenalectomy performed for a suspected adrenal tumor which could not be found. In spite of large dietary supplements of potassium, a positive balance could not be achieved. The patient remained alkalotic with a low serum potassium and had severe polyuria, weakness and bouts of tetany. While on a constant potassium intake the sodium intake was sharply reduced. Balance data were unfortunately incomplete, but the low sodium intake was followed by the almost complete disappearance of sodium from the urine, an increase in potassium balance with a rise in the serum level, and a dramatic improvement in symptoms. It is obvious, that it was only when sodium was in short supply that the patient was able to conserve potassium. It has been suggested that patients with congestive heart failure have a decreased tolerance for potassium on the basis of this same mechanism. The experimental counterpart has been intensively studied by Laragh and Capeci[12] who showed that dogs became intolerant to potassium salts following sodium depletion. A ready explanation, of course, was that hyperkalemia developed because of a decreased capacity of the kidney to excrete this ion. However, careful balance studies have recently shown that the secretory mechanism is normal in the sodium depleted dog[13]. The situation is obviously complex and an explanation for the apparent discrepancies is not immediately available.

Let us now consider the role of the hydrogen ion in potassium secretion. The concept of competition was evolved from acute experiments in which potassium loads increased potassium excretion and were associated with decreased secretion of hydrogen ion. Conversely, an acute alkalosis decreases the availability of hydrogen ion and is associated with an increase in potassium secretion. While this was originally described as a type of competition at the specific site of cation

exchange, subsequent studies suggest that it may be a reflection of changes in the composition of intracellular fluid[14]. From many different types of experiments it has been shown that the intracellular concentration of potassium and hydrogen are so related that a rise in one tends to produce a fall in the other[2, 15, 16]. As examples, let us consider how the composition of the urine would be changed by acute alkalosis and compare this to the effect of a potassium load. In respiratory alkalosis there is of course a fall in hydrogen ion concentration in the plasma and presumably this also occurs in intracellular fluid. Potassium moves into cells, and now at our exchange site potassium has increased, hydrogen has decreased. Thus the chance for a sodium-potassium exchange has increased; that for a sodium-hydrogen exchange decreased. In terms of over-all balance, potassium is excreted in an alkaline urine.

Compare this to the potassium load. This ion is rapidly taken up by the cells, and some of this uptake is in exchange for hydrogen. Thus intracellular potassium rises and hydrogen falls. The chance for a potassium ion to exchange with sodium is thus increased, and in the voided urine we observe an increase in potassium and a decrease in hydrogen. Qualitatively, at least, the changes in urine composition are the same whether we start with alkalosis or a potassium load.

Even if we grant that this scheme is an over-simplification of what undoubtedly must be extraordinarily complex mechanisms, it nevertheless appears valid in a number of situations. However, I would like to point out that it is based on acute short-term experiments and may appear inadequate in a chronic situation. Indeed, there are many instances in renal physiology where it is difficult to extrapolate from an acute experiment to a chronic one. For example, sodium bicarbonate infusions markedly increase the renal excretion of potassium. Recently, Sanderson[17] has studied the chronic response of patients to massive loading with alkali. These subjects had peptic ulcers and received sodium bicarbonate by continuous gastric drip for periods up to three weeks. Initially, 1,000 mEq of bicarbonate per day produced a slight negative potassium balance, but thereafter the patient remained in normal balance. Clearly, physiological adjustments took place which can not adequately be described by the simple scheme that I have discussed. Possibly, these adjustments reflect changes in adrenal cortical secretion, but measurements are not available.

I would now like to consider the second topic, namely, the effect of

potassium depletion on the kidney. Quite a few years ago Ferrebee and his associates[10] produced a "diabetes insipidus-like" syndrome in dogs depleted of potassium by DOCA. More recently, Relman and Schwartz[18] have studied a similar syndrome in patients with gastrointestinal disturbances. On the basis of many experimental and clinical studies it is now clear that potassium depletion produces a fairly definite and reproducible disturbance in renal function, and that this disturbance is essentially the same whether the potassium has been lost through the kidney or by extrarenal routes. The etiological role of potassium seems established beyond a reasonable doubt since the entire syndrome can be reversed after a normal potassium balance has been established. These patients often have other symptoms such as weakness and bouts of paralysis[19].

The renal disturbance is characterized as follows: First, polyuria, nocturia and polydypsia may be quite severe and are frequently the patient's chief complaint. The urine resembles that of diabetes insipidus in that it is hypotonic. While there has been some speculation that the thirst mechanism may also be disturbed, the fact that the urine does not become hypertonic after adequate doses of antidiuretic hormone is a cogent argument that there is a defect in the reabsorption of water by the renal tubule.

Secondly, there is no significant nitrogen retention and although PAH transport may be impaired, there are only minor changes in renal blood flow. Clearance measurements indicate either no impairment or only a moderate reduction in filtration rate. Renal hemodynamics as measured by the clearance of p-aminohippurate are not greatly affected. However, a disturbance in the tubular transport of PAH has been demonstrated by decreased extraction ratios, by a decrease in the T_M, and by the failure of PAH accumulation in the kidney slice system[18, 20].

It is clear then that the syndrome is characterized mainly by alterations in tubular function. Of interest is the effect on urinary acidification. Under most circumstances potassium depletion is associated with an extracellular alkalosis. Darrow, Cooke and others[15] have clearly shown that this can be attributed to shifts of hydrogen ion between the intra- and extracellular fluids and that it can occur without changes in external balance. Hence, although the kidney does not appear essential for the development of the alkalotic syndrome, renal regulation of acid-base balance must be readjusted to permit the extracellular alkalosis to

persist. For example, when alkalosis is produced by the administration of sodium bicarbonate, the normal kidney quickly increases bicarbonate excretion, the urine becomes alkaline, and the plasma bicarbonate level returns to normal. However, in the potassium depleted state this does not occur and extracellular alkalosis is accompanied by the excretion of an acid urine. This so-called "paradoxical aciduria" seems well explained by the tubular mechanism. Unfortunately, direct analyses of kidney tissue are inconclusive and we must proceed from indirect evidence. It is believed that there is a decrease in intracellular potassium in some critical segment of the renal tubule. There is a corresponding increase in intracellular hydrogen ion, and thus, although there is an abnormally high concentration of bicarbonate in the glomerular filtrate, the intracellular relationships are such that sodium-hydrogen exchange is favored, bicarbonate is thus reabsorbed, and the urine is acidified. In many patients, when potassium balance is restored by adequate therapy, the metabolic alkalosis is promptly corrected. Two mechanisms may contribute. First, a redistribution of hydrogen ion between cells and extracellular fluid; and secondly, the increased excretion of bicarbonate in the urine. In a sense, both of these phenomena are a reflection of the same mechanism. The specific role of potassium is well illustrated by the patient of Broch[21]. Parodoxical aciduria was manifest by a persistently acid urine despite marked extracellular alkalosis. Numerous combinations of salt were administered without effect. Potassium was then given and presumably was taken up by the cells of the renal tubules, the local acidosis was corrected, and the tubule then responded to the high load of filtered bicarbonate by excreting an alkaline urine.

Recently, it has been claimed that the potassium depletion of primary aldosteronism is characterized by the excretion of a neutral or only faintly acid urine. How can we reconcile this observation with the scheme just presented? It should be recalled that the pH of the urine is but one manifestation of the acidification mechanism, and that this is directly related to the urinary concentrations of ammonia and of titratable acid. In the normal subject most of the hydrogen ion in the urine is represented by titratable acid and the smaller portion by ammonium ions. The reverse situation seems to be true in potassium depletion. That is, a relatively greater proportion of hydrogen is excreted as ammonium ion. The addition of this ammonia to the urine keeps the pH closer to neutral[22].

It has been suggested that potassium has a direct effect on ammonia synthesis. Muntwyler's group[23] has demonstrated a marked increase in the renal glutaminase of potassium depleted rats, and this finding certainly fits well with the pattern of urinary acidification that has been observed clinically. However, other factors may well be involved and it would be premature to depict too definite a correlation.

The kidney of severe potassium depletion is also characterized by definite morphological changes. Perhaps the most striking is the development of the foam-cell lesion in the proximal tubule, that is the appearance of large cellular vacuoles which stain for neither fat nor glycogen[18]. Lesions in the distal tubule are less conspicuous but seem definite. In experimental depletion it has been shown by Dr. Jean Oliver[24] that the earliest lesion appears in a localized group of cells in the collecting ducts. At present little correlation can be made between the functional and morphological abnormalities. In addition, moderate proteinuria is a common finding. These abnormalities can usually be reversed by the restoration of the potassium balance to normal. Of even greater interest is the fact that potassium depletion in itself appears capable of producing a focal type of pyelonephritis–both in experimental animals and in human subjects. We shall return to this after considering the clinical syndrome of "potassium losing nephritis".

The problem may perhaps be best considered after a very brief historical survey. In 1944, Brown, Currens and Marchand [25] published a case report entitled "Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis". Several years later Albright's group[26] established a fairly well defined entity of "renal tubular acidosis", a syndrome in which the primary defect appears to be a failure of urinary acidification with the subsequent loss of potassium and other fixed cations. It was suggested that this might be the result of pyelonephritis, and thus when Pines and I[27] reported three cases of this condition several years ago, we were perfectly content to include a patient with a ureterosigmoidostomy, who presumably had pyelonephritis. Isolated reports of "potassium losing nephritis" continued to appear and these patients did not appear to fit into any well established syndrome until Conn,[28] in 1955, reported a patient whose disease was almost completely reversed by the removal of an adrenal tumor containing a high content of aldosterone. Since then, other cases have been reported. The question may now be asked–How

TABLE I—CLASSIFICATION OF PRIMARY DEFECTS IN "POTASSIUM LOSING NEPHRITIS"*

A. Definitely not renal
   1. Primary aldosteroma
   2. Cushing's disease
   3. Steroid therapy
   4. Aldosteronism of edematous states(?)
   5. Secondary to metabolic alkalosis
      a. Excessive alkali
      b. Gastric alkalosis

B. Probably not renal
   1. Ureterosigmoidostomy

C. Probably renal
   1. Renal tubular acidosis
   2. Fanconi's syndrome
   3. Acute renal insufficiency—recovery phase
   4. Chronic renal insufficiency(?)
      (Glomerulo-nephritis, pyelonephritis, etc.)
   5. Nephrosis(?)
   6. "Potassium losing nephritis"(?)

* "Potassium losing nephritis" is considered here as a state associated with an abnormally high renal clearance of potassium sufficient to produce a negative potassium balance.

many separate conditions are there that fall under this general heading of "potassium losing nephritis"?

This classification (Table I) contains many conditions which obviously are not primarily renal in origin but which are included because they may readily mimic certain features of a primary renal disorder. The syndrome of renal tubular acidosis is characterized by depletion of both calcium and potassium. The pathogenesis is unknown but the clinical picture is quite characteristic with acidosis, a high plasma chloride, evidence of potassium depletion and the clinical finding of osteomalacia.

This picture of renal tubular acidosis is very similar to the disorder that occurs following ureterosigmoidostomy. Although it was quite reasonable to attribute the latter to renal dysfunction, there is increasing evidence that this disorder is primarily the result of alteration in the function of the colon. First, electrolytes exchange across the mucosa of the colon leading to reabsorption of chloride and of sodium, and to the secretion of potassium[29, 30]. These exchanges occur normally but their importance becomes greatly increased when urine is diverted into

the lumen of the colon by the surgical procedure. Secondly, the clinical syndrome appears to depend upon the prolonged contact of urine with the intestinal mucosa. When stasis is avoided, either by rectal tubes, or by modified surgical procedures, the entire electrolyte disturbance may be easily prevented[31]. Although the evidence strongly indicates an intestinal origin of this disorder, it is clear that the kidney becomes secondarily involved as a result of potassium loss. In a recent series, in 30 per cent of the cases the kidneys showed the lesions of potassium depletion[32]. While some of this loss is undoubtedly from the colon, renal tubular secretion may also play a role. As a result of colonic absorption, the kidney has to excrete much more sodium than is eventually lost from the body, and the kidney is therefore constantly operating under the influence of an exceptionally large sodium load. This facilitates potassium secretion.

Although severe chronic renal insufficiency may be associated with hyperkalemia, there are not sufficient studies to permit one to characterize the potassium balance during the entire course of renal failure. However, the reports that are available suggest that the kidney loses its ability to adjust to variations in potassium intake. Considering this in terms of potassium wastage, it is probable that there are many patients with chronic renal failure who will mimic "potassium losing nephritis" if they are considered at only a single point during the course of their illness. Nephrosis is included in Table I because of the most unusual recent case report of Stanbury and Macaulay[33].

Let us now re-ask the question—Is there such a thing as potassium losing nephritis?—and let us define this as a condition in which excess potassium excretion is either the only demonstrable defect or at least is the overwhelmingly important one. If we answer this question by case reports from the literature, there appear to be few patients who by exclusion seem to fall into this group—at least they have no other demonstrable cause for severe potassium depletion[6, 34-36]. On the other hand, if we try to answer it in terms of physiological mechanisms, we encounter a very confused picture—confused primarily because the causes and the results of electrolyte imbalance can so readily mimic each other. Thus, pyelonephritis might give rise to potassium depletion which in itself might augment renal damage. However, if we postulate as the primary abnormality that a specific tubular defect causes a negative potassium balance, the final picture may be quite similar to primary

pyelonephritis, both as regards functional as well as morphological abnormalities.

In summary, I would emphasize that our knowledge of many of these conditions is woefully inadequate. However, it is an area in which there is wide interest and we can anticipate early clarification of some of the problems not only by fundamental research in the laboratory, but in particular, by the very careful study of a relatively small number of patients who suffer from these disorders.

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THE DISSEMINATION OF CANCER CELLS*†

The Twelfth James Ewing Memorial Lecture

WARREN H. COLE, STUART ROBERTS, ALVIN WATNE, GERALD McDONALD and ELIZABETH McGREW

I WISH first to express my appreciation for the great honor your committee conferred on me by inviting me to give the Annual James Ewing Lecture. It is a distinct privilege indeed to honor Dr. Ewing because scarcely anyone has contributed more to the basic knowledge of cancer than he did. We are fortunate indeed to have had a brilliant scientist like Dr. Ewing devote his entire life to cancer, because maximum contributions can scarcely be made to such a difficult problem without intense devotion of this type. Although his splendid contributions to the various problems in cancer were numerous, perhaps his greatest contribution lies in the devoted inspiration imparted to the multitude of his pupils and associates. We are ever grateful that men of this type have chosen to devote their lives to such an important cause.

Recurrence at the Suture Line Following Colectomy For Cancer.— Our interest in the dissemination of cancer was initiated several years ago by the high incidence of recurrence at the suture line following resection of the colon. In our initial publication[1] we studied 55 cases; in 10.9 per cent of these the local recurrence was so located that implantation appeared to be the most likely explanation. A few years later we studied a larger series of 114 cases. In this study[2] we found almost the same incidence (9.9 per cent) of recurrence at the suture line, best explained on the basis of implantation. Goligher, Dukes and Bussey[3] were also disturbed by the high incidence of local recurrence and in a series of 162 patients having anterior resection of the rectosigmoid for cancer, they found local recurrence in 10 per cent of their series and concluded that implantation was the most likely explanation in

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† From the Departments of Surgery and Pathology, University of Illinois College of Medicine, Chicago, Illinois. Credit is hereby extended Ruth McGrath for valuable technical assistance. Supported in part by grants from the Chicago Community Trust (Rosa Kuhn Levey Fund) and the Illinois Federation of Women's Clubs.

half. However, credit for first emphasizing the importance of implantation of cells in the lumen of the bowel into the suture line after resection should go to Morgan and Lloyd-Davies.[4] In our estimation, if implantation is the mechanism by which local recurrence is produced, it is best explained by the cells being transplanted from the lumen of the bowel into the wall by the suture. While direct implantation into the cut end of the bowel is possible, it does not appear so likely because the cut surface of the bowel would not appear to be as good a medium as the interior of the bowel wall where the suture had been inserted.

We have no proof that implantation is the explanation of local recurrence in the studies reported above, but there are several possible reasons why this should be the best explanation. In the first place, the recurrences occur most often at the suture line. Furthermore, carcinoma does not travel in the wall of the colon as it does in the stomach. It is well known that spread by lymphatics and direct invasion rarely extends distally more than three or four cm.; all capable surgeons resect more normal bowel (beyond the edge of the tumor) than this. Lastly, if the recurrence developed because of residual unexcised tumor in the proximal segment, we should see more recurrences in our colostomies. All surgeons are aware of the extreme rarity of recurrence at this site. Moreover, demonstration of silk sutures in the center of these recurrences (as described later) would appear to support the idea that implantation is a major factor. Black and Kelly[5] have recently studied 116 recurrent lesions following resection of the upper rectum (with preservation of the sphincter) performed between 1940 and 1949 at the Mayo Clinic. In 109 cases, the lesion extended into the lumen of the bowel. Of the 75 cases in which the location of the recurrence was known, the recurrence "developed clearly at the site of anastomosis in 55, below the level of the anastomosis in 12, and within the perineum or at the level of the levators in eight". Lofgren,[6] studying the cases in this series concluded that "the recurrences could best be explained in fully 75 per cent of cases on the basis of implantation". The fact that in their series "recurrences at the site of anastomosis were no more frequent in cases in which lymph nodes were involved than in those without nodal involvement suggests strongly that unresected involved nodes are not responsible for the recurrence". Over a two year period Fleischner and Berenberg[7] made roentgenologic and pathologic examinations in 10 patients with recurrence at the suture line following

resection of the colon; in two cases there was a second recurrence, and in one a third recurrence was identified at autopsy. In three of the patients they found a silk suture in the center of the tumor. They concluded that implantation was the most likely cause of the recurrences.

Studies conducted by us[8] on the presence of malignant cells in the lumen of the bowel after resection of the tumor offer additional evidence that implantation may be the cause of these recurrences. For example, when we ligated the colon above and below the tumor before its resection, and made smears of the lumen in the surgical pathology room within an hour following excision of the specimen, we found that smears taken outside the ligatures were negative, but inside the ligatures the smears were positive in 42 per cent of the proximal ends, and positive in 65 per cent of the distal ends. In general, the incidence of positive smears decreased as the distance between the tumor and the area from which the smear was taken increased. Our success in demonstrating these cells, and those studied since that time, was made possible by the epochal pioneering work of Papanicolaou and Traut.[9] Numerous investigators[10-12] have reported finding cancer cells in washings from the rectal lumen.

Implantation of cancer cells per se into a wound is not a new observation. Perhaps the credit for the first warning of this danger should go to Ryall[13] (1907) who recognized this possibility and actually advised changing drapes, instruments, etc. after a biopsy was performed, before proceeding with the radical resection of the cancer.

Viability of Cancer Cells Desquamated from Tumors of the Colon and Rectum.—Questions have been asked as to whether or not cells desquamated from a tumor of the colon or rectum will live. Considerable data have already accumulated in the literature indicating that these desquamated cells are viable. Guiss[14] reports a patient who had excision of a sinus tract or fistula in ano of two months' duration. Pathologic examination of the excised fistula revealed an adenocarcinoma. Two months later, an abdominal operation was performed, searching for a tumor in the bowel. A tumor of the sigmoid colon was found 20 cm. above the fistulous tract and a Miles resection was performed. There were no metastases. Microscopic examination revealed an adenocarcinoma as in the fistulous tract.

Guiss concluded that the tumor in the fistula was an implant from the tumor located in the low sigmoid, because it was the same type of tumor, and no metastases were found. Besides, metastasis of the usual type this far distal to a tumor of the sigmoid is practically unheard of. In another publication, Beahrs, Phillips and Dockerty[15] report three patients who developed adenocarcinoma in a hemorrhoidectomy wound and one patient who developed an adenocarcinoma in the ulcerating surface of a hemorrhoid. All four of these cases had a carcinoma of the upper rectum or sigmoid which was removed after the hemorrhoidectomy was performed. They concluded that the carcinoma in the anal region had developed from implanted cells arising from the tumor in the rectosigmoid or sigmoid.

Implantation of Cancer Into the Wound Following Resection of Malignant Growths.—Ackerman and Wheat[16] have recently made a study of implantation of cancer cells, and report several different types. They reported two instances in which cancer grew out along the tract made by the needle during biopsy (one in 16 days following biopsy for a squamous cell cancer, and another in 9 days following biopsy of a malignant melanoma). This has been reported previously[17] in a patient with cancer of the prostate. Ackerman and Wheat report several other instances of implantation, including one in a skin graft following radical excision of the breast with skin graft, one in the donor site following a skin graft to the chest wall, one on the peritoneal surface two and one-half years following excision of a carcinoma of the ampulla of Vater, one in the abdominal incision a year following resection of a carcinoma of the stomach, one in the perineal wound three years after abdominal perineal resection of a carcinoma of the rectum, and one in the suture line 18 months after a resection of the colon. In this latter case, a second resection was performed. In the resected specimen no involved nodes were found, but a silk suture was found in the recurrent tumor.

Brandes, White and Sutton[18] also report an instance of implant into the region of the skin graft following radical resection for a cancer of the breast. In this case the operator had washed his hands in distilled water after the mastectomy before the skin graft, but had not changed his gloves. Saphir[19] has identified tumor cells on knives used in surgical

Figure 1.—This patient, a female aged 49, has an implant in the scar of a radical mastectomy performed 4½ years ago. Even though the mass was noted first only four months ago the recurrence appears definitely to be an implant, since all breast tissue was removed from this area.

biopsy or excision. Frantz[20] has reported two instances of local recurrent papillary carcinoma of the thyroid following aspiration. Mayo[21] reported a local implant in the wound adjacent to the colostomy seven weeks after the radical resection of the rectum for cancer. Dvorak[22] reported a local recurrence in the abdominal scar line 13 years after operation for an ovarian cancer.

We have encountered three patients who developed local recurrence in the perineum 6 to 24 months following a Miles resection for carcinoma of the rectum. No evidence of metastases was present in any of the three patients, so the tumor mass was excised. We feel quite sure that implantation into the wound during its original excision represented the source of the recurrence in these three cases. Local recurrence in the scar line following radical mastectomy is fairly common, being reported in 5 to 12 per cent of patients having this operation. Figure 1 illustrates one which developed in our own series. In a patient recently observed by us we did an abdominoperineal resection for carcinoma of the rectum, but had to reoperate the patient six months later to revise her colostomy. A startling observation at this operation was the

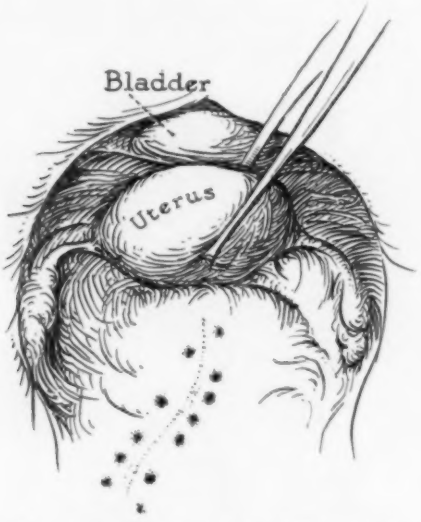


Figure 2.—This patient had a Miles operation for carcinoma of the rectum 18 months ago. Five months later she had an operation to revise her colostomy. At this operation numerous small peritoneal implants were noted on the peritoneum of the lower abdomen, but more dramatic were the small implants in the peritoneum of the pelvic floor, at points where the needle had penetrated during its closure.

presence of small recurrent nodules in the perineal floor almost in every area where our needle had pierced the peritoneum during closure (Figure 2). Figure 3 illustrates a recurrence in the wall of the duodenum following a local resection of a malignant polyp of the ampulla of Vater.

The recent publication of Hilberg and associates[23] in which they report finding cancer cells in 34 per cent of washings from wounds in patients having radical operations for cancer, and atypical cells in an additional 16 per cent, also raises the question as to whether these cells are viable, particularly since no gross cancer was seen or cut across during the resection. The evidence presented by Hilberg and associates suggested that at least many of these cells are viable. The report of White[24] also indicates that these cells are viable and dangerous. He performed a biopsy on a patient with a tumor of the breast, closed the wound, changed all instruments, drapes and gloves, then proceeded

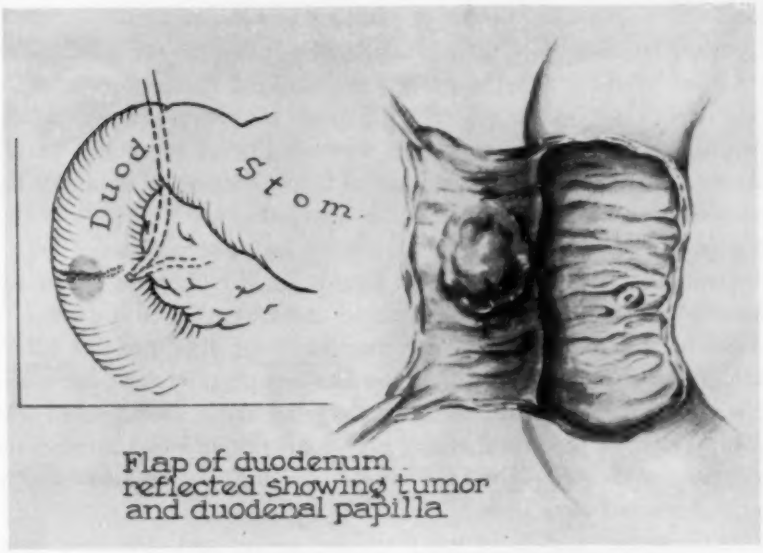


Figure 3.—This patient had a malignant polyp at the sphincter of Oddi excised through a duodenal incision. Seven months later another operation was performed because of gastro-intestinal bleeding and an x-ray deformity. A mass 2 x 3 cm. was found in the suture line (see insert) of the duodenotomy performed seven months previously. Resection of the duodenum and head of the pancreas was performed. The artist has illustrated the location of the mass by constructing a flap in the duodenum. The origin of the mass appears definitely to be implantation during removal of the malignant polyp, particularly since the original site of the tumor was free from tumor (courtesy Thomas Sellett).

with the radical mastectomy. The operator did a skin graft without changing gloves until after the mastectomy. Three months later the patient developed a recurrence in the donor site from which the skin graft was obtained. Presumably, the only sources of the cancer cells were the gloves and instruments contacting the tissues during the operation at which time no gross tumor was seen or cut across. Cells must have been present in the lymphatic or venous channels, and probably were dislocated into the wound during the radical mastectomy.

Preventive Technical Measures Utilized in Human Cancer.—After resection of a malignant tumor, most surgeons irrigate the wound with saline, hoping to remove any "loose" cancer cells which may be present.

A few groups are experimenting with the use of anticancer agents locally as irrigants, but no definite data are available as yet.

After we discovered such a high incidence of local recurrence after resection of the colon for cancer, and realized that implantation of cells into the suture line might be the cause, we resorted to the application of ligatures several centimeters above and below the tumor, before manipulation incident to resection was begun, hoping to minimize the possibility of inoculation of cells into our suture line.[1] This procedure was performed just as soon as operability was determined and before the resection was begun. We have already listed findings in the smears taken inside and outside these ligatures indicating that this procedure might be effective in minimizing inoculation of cells into our suture line. If inoculation into the suture line does take place by this mechanism, it is presumably done by the suture dragging viable desquamated cells into the wall of the bowel where the vascularity affords a satisfactory medium for their growth. They would obviously not be inoculated in normal mucous membrane.

To prevent seeding in the peritoneal cavity and elsewhere from the serosal surface of the bowel containing the tumor, Pomeranz and Garlock[25] have devised a cover for the tumor in the colon during its removal, thus minimizing the possibility of desquamation from the tumor and implantation throughout the peritoneal cavity.

To prevent venous emboli from travelling from the tumor to the liver or lungs, we have recommended ligation of the vascular trunks leading from the tumor area, before any operative manipulation is carried out. This is most readily carried out in resections of the colon, particularly the right side.[2] The ileocolic, right colic, and right branches of the middle colic arteries and veins are ligated as soon as operability is determined, and before operative manipulation is begun.

Prevention of "Takes" in Animals Inoculated with Tumor Cells.— When we realized from the clinical data referred to above that cancer cells might be dislocated by operative manipulation, we developed the idea that anticancer agents which at present will not destroy advanced cancer with vascular attachments, might destroy "loose" cells without a vascular attachment. To test this out in animals we used the Walker rat carcinosarcoma 256, and injected a suspension of cells (110,000)

TABLE I

Effect of one dose (0.5 mg. per kg. of body weight) of Nitrogen Mustard by one of three mechanisms, to rats having Walker 256 cancer cells injected into the portal vein less than one hour previously. (After Cole et al. in Ann. Surg. 145:624, 1957. Reprinted by permission.)

Group	*R Via Portal Vein*		*R Via Per. Cavity*		*R Via Systemic Vein*	
A	No. Rats	% "Take"	No. Rats	% "Take"	No. Rats	% "Take"
110,000 cells	C 48	91.7%	C 45	86.7%	C 45	75.6%
Injected	T 45	17.8%	T 46	41.3%	T 56	35.7%
	Dif.=73.9%		Dif.=45.4%		Dif.=39.9%	
B						
220,000 cells	C 40	82.5%	C 57	82.5%	C 35	94.3%
Injected	T 37	27.0%	T 66	66.5%	T 38	78.9%
	Dif.=55.5%		Dif.=16.0%		Dif.=15.4%	
C						
Combination	C 88	87.5%	C 102	84.3%	C 80	83.8%
of A & B	T 82	22.0%	T 112	57.1%	T 94	53.2%
	Dif.=65.5%		Dif.=27.2%		Dif.=30.6%	

C=Control, T=Treated Animals

TABLE II

Effect of one dose (2.0 mg. per kg. of body weight) of thiotepa given by one of three mechanisms, to rats having Walker 256 cells injected into the portal vein less than one hour previously. (After Cole et al. in Ann. Surg. 145:624, 1957. Reprinted by permission.)

Group	*R Via Portal Vein*		*R Via Per. Cavity*		*R Via Systemic Vein*	
A	No. Rats	% "Takes"	No. Rats	% "Takes"	No. Rats	% "Takes"
110,000 cells	C 30	90.0%	C 38	92.1%	C 39	92.3%
Injected	T 28	7.1%	T 39	17.9%	T 37	16.2%
	Dif.=82.9%		Dif.=74.2%		Dif.=76.1%	
B						
220,000 cells	C 70	61.4%	C 29	75.9%	C 38	94.7%
Injected	T 73	24.6%	T 28	14.3%	T 39	38.4%
	Dif.=36.8%		Dif.=61.6%		Dif.=56.3%	
C						
Combination	C 100	70.0%	C 67	82.1%	C 77	93.5%
of A & B	T 101	19.8%	T 67	16.4%	T 76	27.6%
	Dif.=50.2%		Dif.=65.7%		Dif.=65.9%	

C=Control, T=Treated Animals

TABLE III

The prophylactic effect of one dose of Nitrogen Mustard (0.5 mg./kg.) given intravenously before 110,000 cells were injected into a tributary of the portal vein.

Time of Therapy	*No. of Rats*	*% Takes*	*% Difference*
6 hours before inoculation of cells	C 22	87	
	T 25	80	7
1 hour before inoculation of cells	C 49	94	
	T 47	79	15

C=Control, T=Treated Animals

into the portal vein of rats to simulate the formation of hepatic metastases from gastrointestinal cancer in the human being. We first tried Azaserine but this drug did not have any effect on the percentage of "takes" in the liver of the inoculated animals. We next tried nitrogen mustard (in a single dose of 0.5 mg. per kilo) which was effective in minimizing the percentage of "takes"; thiotepa is slightly more effective[26,27] (Tables I and II).

Although certain anticancer agents are effective in preventing the "takes" of Walker 256 cells when injected into the portal system within an hour after inoculation of the cells, it would be important to know what the effect would be if treatment was delayed, particularly if clinical application is to be made of these data. Accordingly, we varied the time between therapy and inoculation of cells and vice versa. As shown in Table III, there was very little effect on the percentage of "takes" when the HN_2 was given before the inoculation of cells. The effect obtained by using HN_2 might be different with other anticancer agents because it acts within a few minutes and does not build up a blood level. When the HN_2 is given six or more hours after inoculation of cells, there is also only slight effect on the percentage of "takes" (see Table IV).

Dissemination of Cancer by Venous Emboli.—The growth of carcinoma into the veins within a tumor has been called to our attention by pathologists for years; but surgeons, in general, have not been fully

TABLE IV

The prophylactic effect of one dose of Nitrogen Mustard (0.5 mg./kg.) given intravenously after 110,000 cells were given into a tributary of the portal vein.

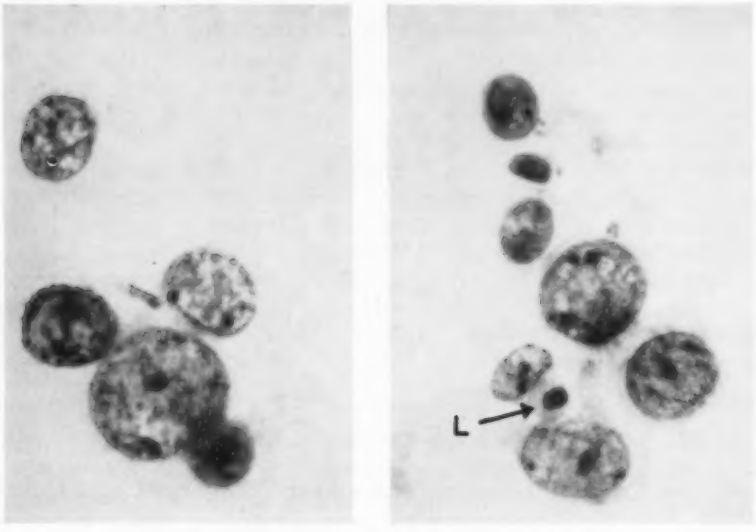
Time of Therapy	*No. of Rats*	*% Takes*	*% Difference*
48 hours after inoculation of cells	C 42	90	
	T 39	85	5
24 hours after inoculation of cells	C 42	81	
	T 40	73	8
6 hours after inoculation of cells	C 27	100	
	T 27	89	11

C=Control, T=Treated Animals

aware of the danger of this phenomenon. Many years ago, Dukes[28] reported finding invasion of veins in 17 per cent of tumors in patients having rectal carcinoma, and slightly less in lesions of the colon. In a study of specimens removed at operation Grinnell[29] reported an incidence of venous invasion in 36 per cent of patients with rectal carcinoma, and in 33 per cent of patients with colonic carcinoma. Brown and Warren[30] reported an incidence of venous invasion in 61 per cent of autopsy specimens obtained from patients with rectal carcinoma; one would expect the incidence to be higher in such cases, since the tumor would usually be far advanced.

In Grinnell's series referred to above, the five year survival rate was 37 per cent in patients with venous invasion, and 76 per cent in patients without venous invasion. This corresponded closely to the relationship of lymph node metastases to five year survival, which was 41 per cent in patients with node metastases and 83 per cent in patients without node metastases.

Barringer, Dockery, Waugh and Bargen[31] conducted a study of venous invasion in colonic carcinoma by injecting the veins with an opaque medium (warm brominol) and taking a roentgenogram. In this series 51 per cent showed venous occlusion by roentgenogram, whereas 38 per cent of the specimens revealed microscopic invasion of veins. It is remarkable that these workers were able to find obstructed



(a) (b)

Figure 4.—Carcinoma of the breast (Papanicolaou stain, X 1100) a.—Malignant cells from a direct smear of the resected tumor. b.—Malignant cells isolated from peripheral blood (anti-cubital vein) during the skin preparation incident to operation. The similarity of the groups is striking and would appear to leave no doubt that the cells obtained from the systemic vein are malignant. L=lymphocyte.

veins by roentgenogram, and then locate them so accurately that they could demonstrate invaded veins microscopically.

In 1953 we conducted experiments[32] perfusing the tumor (colon and rectum) by injecting saline through the artery, and examining the venous return (blood and saline) microscopically. Smears were stained after the method devised by Papanicolaou and Traut.[9] We found cancer cells by this method, and as a result began the procedure of preliminary ligation of vascular trunks (herein described) supplying the tumor area before operative manipulation was begun. Fisher and Turnbull[32] have carried this still further and report finding carcinoma cells in 31.4 per cent of samples of venous blood drainage from the tumor. Turnbull[34] has more recently reported that in 36 patients with colonic cancer operated on by the usual method, cancer cells were found in 28 per cent of cases, whereas in 76 patients having resection without handling

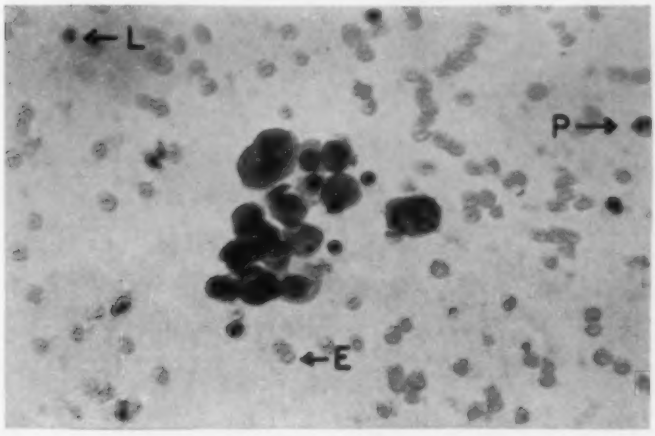


Figure 5.—Carcinoma of the breast (Papanicolaou stain, X 500). Clump of malignant cells isolated from venous blood draining tumor area (subclavian vein through a catheter) preoperatively. Note the size of the malignant cells compared with erythrocytes (E), polymorphonuclear cells (P), and lymphocytes (L).

the tumor during the operation, cancer cells were found in only 13 per cent.

Engell[35] has reported finding cancer cells in blood draining from the tumor in 54 per cent of 76 patients with cancer of the rectum and in 70 per cent of 31 patients with cancer of the colon. Of particular interest in Engell's report are his data indicating that the cytological findings were positive in 35 per cent of Grade II tumors, in 78 per cent of patients with Grade III tumors and in 100 per cent of Grade IV tumors. Engell also found cells in the systemic blood in 7 of 14 patients with inoperable tumors, but in only 10 of 79 patients with operable tumors.

We have continued our search for cancer cells in venous blood by looking for them in systemic blood, and in the blood obtained by a plastic catheter inserted into a major venous trunk (vena cava, subclavian vein, etc.) draining the tumor area. We have modified our original method, now utilizing fibrinogen for precipitating the red cells, layering with bovine albumin and staining by the Papanicolaou technique which we believe is superior to Wright's stain. Utilizing this

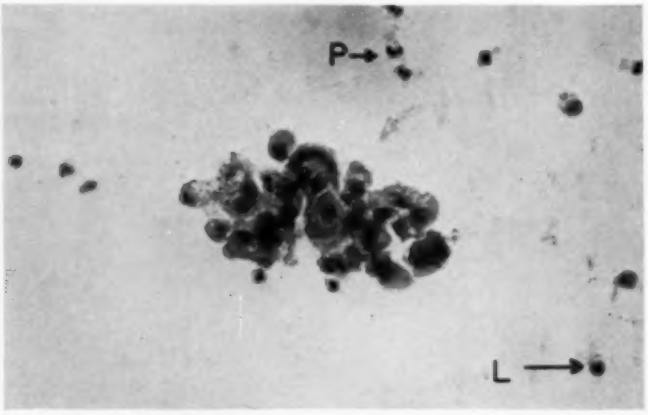


Figure 6.—Carcinoma of the kidney (Papanicolaou stain, X 500). Clump of malignant cells isolated from venous blood draining tumor area (inferior vena cava through a catheter) just prior to application of the pedicle clamp. P=polymorphonuclear, L=lymphocyte. This patient expired six months postoperatively with x-ray evidence of massive pulmonary metastases.

method we have been amazed to find cancer cells in the circulating venous blood of so many patients. By this technique, single cell diagnosis is possible. The cells identified as cancer cells are identical with those obtained by direct smears (Fig. 4). The cells found in the systemic blood are often single cells whereas the cells found in the major venous trunks (obtained by catheter) are usually recovered in clumps (Figs. 5 and 6); this is perhaps to be expected since the cells in the systemic blood have usually been filtered through the lungs and/or other organs. In general, when cancer cells are found in the blood obtained from a major venous trunk by catheter, they are also usually found in the systemic blood (Fig. 7). As would be expected, we usually find more cells in the blood obtained by catheter than in the systemic blood. However, the incidence of cells in the peripheral blood of patients with cancer of the gastrointestinal tract is quite low, suggesting that the liver is a fairly effective filter. There appears to be a direct relationship between the advancing stage of the disease and the percentage of positive blood samples. Although the method is not a quantitative one, we can obtain an idea concerning the number of cells in a given amount of blood, since each sample is processed by the same technique, thus

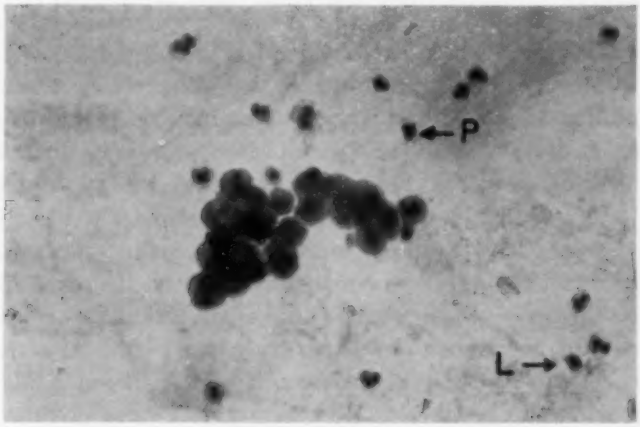


Figure 7.—Carcinoma of the stomach (Papanicolaou stain, X 500). Clump of malignant cells isolated from peripheral blood (anti-cubital vein) preoperatively. P=polymorphonuclear, L=lymphocyte.

allowing comparison. Data assembled up to date suggest that surgical manipulation increases the number of cancer cells found in the blood. Most of the patients having positive peripheral blood samples have had adenocarcinomas or transitional cell carcinomas. Surprisingly, in certain far advanced fast growing carcinomas (e.g., carcinomas of the gallbladder) no cells are found. It is possible that the cells of these tumors resemble the lymphoid cells so closely that we are not able to separate and identify them. Complete removal of the cancer (by operation) results in disappearance of cancer cells from the blood, although it may not if residual tumor metastases remain. The blood of patients with benign lesions has been negative.

The comparatively large number of malignant cells found in the circulating venous blood by us and others[35, 36] during the past year or two has raised the question as to whether or not these cells are viable. Yet it is obvious that some of them survive, otherwise we would have no venous metastases. Viability could be related to any or all of three factors: 1) number of cells; 2) virulence of the cells; and 3) host resistance. An enormous amount of work will be required to determine which factor is the most important. It is probable that each plays a role, but varying in degree from patient to patient.

Prophylactic or Adjuvant Treatment of Human Cancer. As soon as we noted that nitrogen mustard would appreciably minimize the percentage "takes" when given within an hour after inoculation of Walker 256 cells into a branch of the portal system[26] we began using it in human patients with four types of tumors (colon, rectum, stomach, and breast) which notoriously metastasize by way of the vascular system. We did so on the assumption that an operation may disseminate cancer cells and that if nitrogen mustard and thiotepa are as effective in preventing "takes" in human patients as they are in animals, the incidence of metastases might be decreased. We injected our first patient in March 1956. We were of course aware of the toxic action of nitrogen mustard, including the serious depressing effect on the bone marrow. We expected that the toxic effect of nitrogen mustard would be greater when it was given at the time of operation than when given at other times, and found this to be true. The chief reason for this increased toxicity lies in the tendency for this agent to induce bleeding (from the wound), and the increased tendency for development of infection (especially wound) because of the bone marrow depression.

Up to the present time we have given nitrogen mustard to about 65 patients at the time of operation. Of this number 36 were treated for gastrointestinal carcinoma. Most of the remaining patients had carcinoma of the breast. The complications in the 36 patients are listed in Table V. In brief, four of the 36 had a leukopenia below 3000, four had excessive bleeding after operation, two had an unusual degree of postoperative ileus and one developed a wound abscess.

One patient in this series died 11 days after an abdominoperineal resection of the rectum for cancer. She received only one dose of nitrogen mustard (6.5 mg. intraperitoneally at the end of the operation), but was not given any more because on the day after operation she developed a severe diarrhea caused by a staphylococcic enteritis. In spite of diligent efforts to control the loss of fluids and electrolytes, she died. Since the patient received only one dose of mustard (6.5 mg. or 0.1 mg. per kilo) we do not believe the anticancer therapy had anything to do with her death, particularly since her white count was not decreased below normal. The average need of treated patients for blood during operation in the postoperative period before discharge was 918 cc. more per patient in the treated group than in the controls. Since excessive bleeding occurred in only 4 of the 36 patients (300 to

TABLE V

COMPLICATIONS WITH HN_2 GIVEN AS ADJUVANT THERAPY

(Dr. C. Branch 6 cases, Dr. W. Eastman 2 cases, Dr. A. Curreri 2 cases)

		Complications			
Type of Operation	*No. of Cases*	*Leukopenia (<3,000)*	*Bleeding*	*Ileus*	*Infection or Obstr.*
Colectomy	23	4	3	1	1
Gastrectomy	2	0	0	0	0
Miscellaneous	5	0	0	0	0
Celiotomy only	6	0	1	1	0
TOTAL	36	4	4	2	1

One death 11 days after operation. Patient was 64 years old, white, female, having abdomino-perineal resection. Had 6.5 mg. HN_2 intraperitoneally, but none thereafter. Profuse diarrhea, electrolyte imbalance. Lowest WBC 6,750. (After Cole et al. presented at the Alkylating Conference, New York, March 28 and 29, 1957.)

600 cc. each) we assume that the bone marrow depression might be an important factor in explaining this blood deficit, although it is possible that some of the patients having celiotomies might have had occult bleeding into the peritoneal cavity.

We lost another patient (one in the breast series) who appeared to have sustained a serious toxic reaction from the nitrogen mustard. She was a mildly obese woman, 79 years of age, who received 0.1 mg. of the drug per kilo on four successive days, including the day of operation. She developed a hematoma in the wound which became infected, later resulting in a septicemia (E. coli). The WBC in this patient dropped to 1500. This reaction has led us to limit the adjuvant use of nitrogen mustard to patients under 71 years of age and to a maximum total dose of 30 mg., in order to eliminate overdosage related to obesity.

Our experience with nitrogen mustard has convinced us that the agent is more toxic when given at the time of operation, but that if certain precautions are taken it can be used safely.[37] As stated, we do not give it to patients over 70 years of age; we give it in a total dose of 0.4 mg. per kg., but limit the total dose to 30 mg. in obese or heavy patients. In view of the marked decrease in efficiency of nitrogen mustard when given 6, 24 and 48 hours after inoculation of Walker 256 cells in the rat, we have assumed that if it is at all effective in destroying "loose" cells dislocated during operation, a fairly large dose

should be given on the day of operation. Our present routine for patients having resection of intraperitoneal cancer (colon, rectum, and stomach) is to give 0.2 mg. per kilo (maximum of 15 mg.) on the day of operation, 0.1 mg. per kilo (maximum of 7.5 mg.) on the first postoperative day, and 0.1 mg. per kilo on the second postoperative day (with a maximum of 7.5 mg. on each of these days). We divide the 0.2 mg. per kilo dose on the day of operation into two doses, one half into a tributary of the portal vein, and one half left in the peritoneal cavity at the end of the operation (through a catheter leading down to the operative site), before the patient leaves the operating room. We have seen no increase in toxicity by giving half the total dose on the day of operation. It might appear advisable to give all of the anticancer agent on the day of operation. If it is given this way, we strongly advise that no more than 0.4 mg. per kilo be given (maximum of 30 mg. total) even though we know of several patients who have received slightly more than this without serious effect. Nevertheless we know of one patient (not ours) who died after having been given 0.6 mg. nitrogen mustard per kilo into the peritoneal cavity at the time of operation; cause of death in this case was an oliguria which presumably was caused by the drug toxicity.

Summary

A few years ago we became disturbed by the large number of recurrences in the suture line following resection of the colon for carcinoma, and, after studying the cases, concluded that most of them were best explained on the basis of implantation, probably by way of the sutures used in the anastomosis. To prevent these recurrences, we advise ligation of the lumen of the bowel above and below the lesion before the operation is begun; we likewise recommend thorough cleansing of the bowel lumen before sutures are placed in the anastomotic line. Also, in order to prevent venous emboli arising from the tumor during operative manipulation we advise preliminary ligation of vascular trunks leading to and from the tumor wherever possible.

Additional experiments in our laboratory support our original findings that nitrogen mustard and thiotepa appreciably minimize the percentage "takes" of Walker 256 cells injected into Sprague Dawley rats, when the drug is given within a few minutes to an hour after inoculation of the cells. However, when nitrogen mustard is given six hours

or one hour before inoculation of the cells, no appreciable effect on the number of "takes" is noted. Likewise, when nitrogen mustard is given 6 hours, 24 hours or 48 hours after inoculation of cells there is no appreciable effect on the number of "takes". The effect of nitrogen mustard and thiotepa is influenced greatly by the number of cells inoculated, in so far as the "takes" are reduced much more when 110,000 cells are injected than when 220,000 cells are injected.

We have now given nitrogen mustard to about 65 patients at the time of resection of a carcinoma (primarily tumors of the breast, colon, rectum and stomach). Two of these patients died after operation. One died 11 days after an abdominoperineal resection for a carcinoma of the rectum; she had only one dose of nitrogen mustard (6.5 mg.) because she developed a severe staphylococcic enteritis the day following operation. We do not believe this fatality can be ascribed to the anticancer therapy. However, another patient, an obese female age 79 having a radical mastectomy, died 13 days after receiving four daily doses of nitrogen mustard (0.1 mg. per kilo), with a wound infection and septicemia. We believe this death was related to the therapy, and as a consequence have limited use of the drug to patients under 71, and limit the total dose to 30 mg., still giving no more than 0.4 mg. per kilo for the total course. We are sufficiently convinced of the safety of nitrogen mustard therapy, using these precautions, that we are now giving half the total dose on the day of operation and one fourth on each of two succeeding days. The primary purpose of prophylactic or adjuvant therapy is to destroy cancer cells dislocated during operative manipulation. However, we hope and believe the proper anticancer drugs will slow down or prevent the progression of dormant microscopic nests of cells to growing metastases.

Examination of the circulating venous blood in patients with cancer has revealed positive smears in a remarkably large percentage of cases. The number of cells is greater in blood samples obtained from major venous trunks (by plastic catheter) than from the systemic blood. Moreover more clumps are found in blood from the former source than from the latter. Most of the positive cases in our series were obtained from patients with adenocarcinoma or transitional cell carcinoma. Removal of the tumor (by operation) has resulted in disappearance of the cells (but may not if metastases are present). We have not found "cancer" cells in patients with benign lesions.

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SURGICAL MANAGEMENT OF CARDIOVASCULAR DISEASE

*Transcription of a Panel Meeting**

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Panel Members

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* Presented at the 29th Graduate Fortnight of The New York Academy of Medicine, October 22, 1956.

MODERATOR LUDWIG W. EICHNA: Ladies and Gentlemen, I want to welcome you to this panel session of the Graduate Fortnight of The New York Academy of Medicine. The topic for discussion today is "The Surgical Management of Cardiovascular Disease".

I should like to introduce the panelists, although I am sure they are all well known to most of you. On your right is Dr. Frank Glenn, Lewis Atterbury Stimson Professor of Surgery, Cornell University Medical College; Surgeon-in-Chief, The New York Hospital; next is Dr. André Cournand, Professor of Medicine, College of Physicians and Surgeons, Columbia University; Director, Cardiopulmonary Laboratory, First (Columbia) Medical Division, Bellevue Hospital. I know it gives us all pleasure to add to this, also, Nobel Laureate in Medicine (Physiology) for 1956, together with Drs. Werner Forssmann and Dr. Dickinson Richards. Next to Dr. Cournand is Dr. Clarence Dennis, Professor and Chairman, Department of Surgery, State University of New York College of Medicine at New York City; Chief of Surgery, Kings County Hospital in Brooklyn.

It is quite difficult to know where to begin on a topic of these proportions. The panel met for a short period to decide on just how to proceed and concluded it might be advantageous to spend more time on those aspects of cardiovascular disease now in the process of development, rather than on those aspects which are well established.

Again, we should consider the problem of management of acquired heart disease, as well as the surgical management of the congenital heart conditions. With your permission, we prefer to start with acquired heart disease.

The panel will welcome any questions that you may have. An usher will collect your written questions and I shall try to address them to the various panelists.

One of the first questions which comes to mind is, what is the present status of cardiovascular surgery for that form of acquired heart disease which has perhaps the longest record of attack? So let us consider the mitral valve.

Dr. Glenn, what is the present status of mitral commissurotomy as the surgeon sees it today?

DR. FRANK GLENN: It is a rather gratifying position at the moment because risk has been decreased and results have improved steadily since surgery has been employed. Over the past ten years several thousand

operations have been done for mitral stenosis and in this period an increasing number of surgeons have begun to use the procedure. Now it is being accomplished with a reasonable mortality rate, a mortality rate that, I believe, is commensurate with other major surgical undertakings. I would say that the over-all mortality rate for the country is probably in the neighborhood of 5 per cent so that we have an operation that is relatively safe for patients. Now, how effective is it? This is more difficult to evaluate, not only as to the immediate results but, what is more important, for the prolongation of life. From a review of the articles that have appeared in the literature during the past year I would say that 75 per cent of the patients are markedly improved and some are only slightly improved. We are probably justified in saying that there is no doubt that over half of the patients derive real benefit from the operation. How many more than 50 per cent I don't know. Occasionally patients have been made worse. Fortunately, they represent a small percentage. This is true for many conditions treated surgically, there will be those who may be made worse or those who may die. If we follow too narrow a channel in approaching the problem then we deprive too many patients of the opportunity to be benefited.

The remaining question, the one that I cannot answer for you at this time is: does this procedure prolong life? In other words, can we, at the end of 20 years, show that we have extended the life expectancy in an individual with mitral valve stenosis? Furthermore, can we correlate valve area, age and life expectancy for those treated by commissurotomy? That is the question that cannot be answered now. I believe that both surgeons and internists are encouraged by what has been accomplished.

MODERATOR EICHNA: This brings us right to the problem of the next question: If the results are as encouraging as Dr. Glenn has indicated, then the important thing is the selection of the patient.

Dr. Cournand, would you like to start the discussion on that point?

DR. ANDRE COURNAND: The selection of patients for surgery should first be left to physicians who should discuss the case with the surgeon. In other words, if a patient is sent by his own physician to a cardiologist to decide whether he should be operated upon, the opinion of the private physician should be taken into consideration by the consultant. Such a step is essential before referring the patient to the surgeon. Patients should not actually be operated upon without a prior en-

lightened opinion of a specialist. I believe too many patients have been referred to surgeons, patients who, in some instances, should not have been operated upon because they had not had the benefit of the best medical therapy. This is my first point.

The second point is that there are certain types of patients in whom there is practically no question as to the surgical indications. Among these are those patients who have definite evidence of pulmonary hypertension as the result of increased pressure in the left atrium and who are greatly incapacitated: shortness of breath of considerable degree, evidence of pulmonary edema and especially those who show continuous and rapidly progressive disability.

The question whether a patient with an early mitral stenosis with very little clinical manifestation should be operated upon is still, I think, not answered. At this time I personally believe that no case demonstrating mitral block without pulmonary hypertension should be operated upon.

Of course, there is a group of patients who are greatly incapacitated who have had some evidence of cardiac failure in the past, sometimes repeated episodes, in whom it is very important to be certain that all the manifestations are due to mechanical block and not to myocardial insufficiency. Dr. Ferrer and Dr. Harvey, in our laboratory, have studied this problem and are very insistent upon the point of view which is gaining more and more support that a patient who has a series of episodes of cardiac failure and in whom at cardiac catheterization the pulmonary pressures are found to be normal, is not primarily a case of block but of myocardial insufficiency.

In this respect there is a very important question to be decided. There are some cases where mechanical block is associated with marked cardiac insufficiency. Will these cases benefit from surgery? This question cannot as yet be answered decisively. Some answers may be found in the questionnaires sent around to former patients who check "yes" and "no" columns concerning benefits derived from surgery. Moreover, these answers are not supported by good physiological data, without which a sound opinion cannot be built. I do believe that objective evidence is much more important than subjective evidence and that physiological studies in such cases would be extremely valuable and helpful in deciding how much benefit the patient has derived from surgery.

MODERATOR EICHNA: Thank you, Dr. Cournand.

I should like to introduce another member of the panel, Dr. F. John Lewis, Associate Professor of Surgery, Northwestern University School of Medicine; Surgical Staff, Passavant Memorial Hospital, Chicago. His arrival from Chicago was delayed because of bad flying weather. We are glad to have you with us Dr. Lewis.

I should now like to ask both Dr. Cournand and Dr. Glenn: Do you insist on physiological determinations by cardiac catheterization before surgery? Dr. Glenn!

DR. GLENN: The first 120-odd patients on whom we performed the operation for mitral stenosis were catheterized and many of those also had angiocardiography done. We did not catheterize those in whom there was a contraindication, where we were fearful of emboli or where there had been a history of emboli. Thereafter we ceased to do this as a regular study and did it only on indication. It seems to me, from our experience with the early series of cases, that we usually found that cardiac catheterization confirmed our clinical diagnosis. I believe that there are times when it is indicated and provides specific and valuable data in those who are diagnostic problems. We had hoped that it would help us settle the problem of the degree of regurgitation when insufficiency and stenosis occurred together but this has not been borne out. So at the present time we employ cardiac catheterization and angiocardiography prior to operation only on indication. We have considered it essential in less than 10 per cent of cases.

MODERATOR EICHNA: *Dr. Cournand, your comments on this point!*

DR. COURNAND: I would agree with Dr. Glenn that in the first group which I described there are clearcut indications that cardiac catheterization is not essential from the point of view of the patient's immediate advantages. Nonetheless, someone should study these cases in series so as to be able to report at a later time about the natural history of the disease and of the long range effects of surgery. This is of course a problem which is slightly different from the problem of immediate benefit to the patient. So I do agree partly with Dr. Glenn. However, there are a number of instances when it is absolutely essential to carry out cardiac catheterization, particularly in those cases that I have previously mentioned, which have a long history of repeated episodes of cardiac failure. There are still large numbers of instances where surgery is carried out on the basis of inadequate study and experience.

With regard to mitral insufficiency, of course, we have to discuss some technical procedures. Tracings which are obtained by wedging a catheter in the pulmonary artery are not always capable of demonstrating a significant degree of mitral regurgitation, although some investigators rely very much on the characteristics of these tracings. In doubtful cases, left heart catheterization should be undertaken. We may have time to say something about this procedure later.

MODERATOR EICHNA: *Yes, Dr. Glenn!*

DR. GLENN: I want to support Dr. Cournand in emphasizing that cardiac catheterization is essential for obtaining data upon which we can depend for demonstrating physiological improvement. As he pointed out, those institutions which are equipped to do so should do a certain number of cardiac catheterizations for study purposes, even though the operation is clearly indicated without it.

MODERATOR EICHNA: *Dr. Dennis, have you a comment on this point?*

DR. CLARENCE DENNIS: Only one, that is, those procedures which have been recommended for the management of insufficiency are all blind operations. All are successful in some cases, but not in as many as one would like to see.

With the thought in mind that it might be useful to do something more definitive about it, Dr. Newman and my associates and I have worked in the experimental laboratory endeavoring to put in a plastic prosthesis in place of the mitral valve in experimental animals. We have a paper which has been accepted for publication which reports the experiments on the first 25 dogs that had such valves put in. We have had many troubles that are so great that it would be unwise to recommend this for a human being who comes in and wants something done. But in dogs we have had survivors that ran as long as three months and held their own in dog fights. They seem to be getting along satisfactorily. However, it does seem that it would be preferable to approach this lesion by direct vision and be able to see what one is doing. One might then be able to fashion the valve that is there so that it might do the job satisfactorily and avoid inserting a prosthesis. We are only about to try that.

DR. F. JOHN LEWIS: For stenosis?

DR. DENNIS: No, not for mitral stenosis. The risk, as Dr. Glenn pointed out, is very low. It would be a great mistake to suggest anything of this sort for anything that can be satisfactorily handled without

the use of a heart-lung machine.

DR. COURNAND: May I say just one word about the word "satisfactory"? We have seen excellent results in patients who had been sent to the hospital for surgery but who had instead been treated by medical means. When these patients left the hospital they felt much better than when they came in. As a matter of fact physiological measurements sometimes indicated definite improvement. I would say that a patient under the control of physicians and taken care of in a hospital for a long period of time cannot be classified as satisfactory as a result of surgery unless physiologic measurements demonstrate striking changes towards more normal values.

MODERATOR EICHNA: *Dr. Lewis, have you a comment on this point?*

DR. LEWIS: No, except I would think that perhaps the results from surgery, whether they are satisfactory or not, are probably not good enough. What we should look for is better surgery for mitral stenosis. It is hard to tell what percentage of patients are helped by the present day operations, as Dr. Cournand has implied, but the most optimistic figures concerning patients followed for five years or so probably indicate that by clinical estimation no more than 50 or 60 per cent are improved over their preoperative status, which is a result that you would think could be improved upon, perhaps by a better operation.

DR. DENNIS: Dr. Eichna, I would like to ask Dr. Glenn one question, if I may. In the last five years I have encountered three patients who apparently have redeveloped tight mitral stenosis after having had a valvuloplasty performed with an apparent satisfactory result after the original procedure. I wonder what Dr. Glenn's experience is with regard to this point in the large series that he has seen.

DR. GLENN: We have not had a large experience with so-called resealing or recurring mitral stenosis but we have operated upon five such patients. One of these patients died two weeks after the second operation following discharge from the hospital. We had a postmortem examination on that patient and I thought it was very clearly demonstrated that his original primary separation of the commissure had not resealed. What apparently had happened was a continuation of the disease involvement of the remainder of the valve. This resulted in a new stenosis for which we were able to increase adequately the valve area at the second operation. I am very skeptical about so-called resealing of the valves. I think there are two explanations for recurrence of

stenosis as we see it today. First, that there is not an adequate operation done at the first procedure and second, there is a progression of the disease that involves the valve, all the valve components, including the ring of the valve. Does that answer your question?

DR. DENNIS: Yes, it does. Two of these patients had acute flare-ups of rheumatic fever after the original operation. It was thought that in these a progression of the disease was observed to take place.

MODERATOR EICHNA: *This discussion has just emphasized, then, that the patient still has rheumatic heart disease. The fact that an operation has been performed does not necessarily mean that all of the life history of rheumatic heart disease is forthwith removed. Do you agree, Dr. Glenn?*

DR. GLENN: Yes, I think that is exactly the situation. I am still quite uncertain in my own mind just what the sequence of events is in a heart valve where we find a great deal of scarring. In a well scarred valve it seems that the process is not active. In others the valve, at the time of operation, feels as though there was something more than scar tissue, i.e., inflammatory reaction. Under these circumstances I am inclined to expect additional changes in such a valve.

MODERATOR EICHNA: I cannot help but express some surprise at the unanimity regarding the ease of choice of patients and how they are chosen for operation. I don't mean to be obstructive but I cannot see what is wrong with performing cardiac catheterization before submitting the patient to a thoracotomy and indeed, in our experience there have been a number of instances in which cardiac catheterization has led us to a different result and procedure.

With that, I would like to ask an impertinent question. Dr. Glenn, how many operations do you suppose are done needlessly for suspected mechanical block due to mitral stenosis today? Then I would like to ask the same question of Dr. Cournand. Dr. Glenn!

DR. GLENN: In the first place, I don't know. There is no doubt that there are many surgeons in this country today who are doing what Dr. Cournand rightly says should not be done. They are accepting patients who are willing to be operated upon and, because the surgeons have the facilities, they proceed with an operation. This does happen in this country, but how often I don't know,—but it does occur.

In an organization or institution that has a well balanced team of cardiophysiologists, internists, cardiologists and surgeons who are con-

scientiously and deeply interested in this problem, I think there will be relatively few unindicated operations performed. I admit that on occasion I have "burned my fingers", because of a wrong diagnosis, even with all the help that I could get from the members of our group, including the cardiophysiologist. However, these instances are few in number.

DR. COURNAND: I may add to this statement that the cardiophysiologist, like the internist and the cardiologist, very humbly recognized that he has received a slap on his fingers when the surgeon and/or the pathologist show him how wrong he can be. No method is infallible and Dr. Glenn has rightly pointed out that in this problem, as in many others, it is teamwork which is important. Teamwork suggests and implies a varied approach to a problem. Even in the case of mitral stenosis in spite of contrary claims, there is much progress still to be made; progress depends on good teamwork.

May I now ask of Dr. Glenn, whether it would not be a good idea to classify the results according to the type of lesions that surgeons observe at the time of operation. Are there not different results in the vascular lesions, depending upon whether the leaflets are still mobile and the free edges rolled up or where they appear as a calcified and flat diaphragm? This differentiation may play an important role in reaching a decision concerning surgery.

DR. GLENN: We very much need specific criteria for classification of disease of all kinds and particularly the mitral valve. It is rather difficult to get an agreement on terms used in describing a valve. This is true even among pathologists; the people who have been most adamant in their description and correlation have been the internists. I think that it probably will come about in time that the pathologist is the one who will set the criterion and the surgeon will acquire enough skill to evaluate it with his index finger and with the data that have been obtained by other means the correlation will go on from there. We very much need that standardization. I am quite sure it will come just as we have finally agreed upon a nomenclature for the development of diseases in general.

DR. COURNAND: I am sure there are a number of patients who are operated upon needlessly and who may present a story similar to the following: A young girl is admitted to the hospital; she is just married; the husband carries her in his arms from the street to the third floor where she lives. She has the physical signs of a mitral stenosis and is sent

to the hospital by her private physician who suggests surgery. To your great surprise she lies flat on her back. All physiologic data indicate that this patient does not require surgery. After a good talk to her and her husband she can walk out of the hospital on her own two feet and even walk quite rapidly. This true story is not exceptional. Iatrogenic symptoms are to be reckoned with. I think every physician has seen that type of case. If such a case had been operated upon I don't doubt for a moment that it would have been classified as an ideal result!

MODERATOR EICHNA: *Dr. Cournand, you have just come from a trip abroad. Would you like to hazard a guess as to how many needless mitral commissurotomies are done, not only here but also abroad? Would you like to put a figure to it? I am going to press you on this point.*

DR. COURNAND: I might have more to say about other surgical procedures which are used abroad than mitral commissurotomy.

As far as the latter operation is concerned, there is fairly good agreement, among the physicians whom I interviewed there, and the ideas which I expressed before. There may be some slight variations as to whether in the face of early evidence of mitral block the patient should be operated on or not. There are also some surgeons who may tend to ignore the cardiologist who has known the case for a long time and who may not be tempted to recommend operation. I don't see that there are very striking differences in the surgical procedure itself between here and abroad. There is possibly as much enthusiasm.

MODERATOR EICHNA: *May I ask what is the present status, then, of mitral commissurotomy for the patient who has a tight valve plus congestive heart failure? Dr. Cournand, do you recommend such patients for operation?*

DR. COURNAND: If it can be demonstrated in such cases, that the myocardial insufficiency associated with a rheumatic process is not present, and therefore that the episode of congestive heart failure is temporary and controllable, then surgery may be performed. In cases of cardiac failure of the right heart type, the patient can be greatly benefited by operation if the mitral block is severe, and pulmonary vascular resistance of moderate degree.

MODERATOR EICHNA: *I would now like to pass to the aortic valve. I think we all recognize that this represents one of the most pressing problems with which the clinician and surgeon will have to contend*

in the next few years. Dr. Lewis, would you like to start the discussion on what we are going to do about the aortic valve?

DR. LEWIS: In a number of respects it is a more difficult valve to deal with surgically than the mitral valve. The pathological changes that occur in the valve are far more apt to involve the entire valve cusp than is the case in the mitral valve. Whereas in the mitral valve you may get fusion of the cusp, which is quite amenable to commissurotomy, by the time you have a fusion of an aortic valve there is usually a serious thickening and calcification of the entire cusp so that any current operation on the aortic valve, or one that could be employed in the near future, is limited in its effectiveness by the pathology of the disease.

The ideal operation for any serious type of aortic valve disease, either stenosis or insufficiency, should be a complete valvular replacement, but at the present time there are, in my opinion, no satisfactory artificial valves. I don't think Hufnagel's valve is quite good enough. Surgeons all over the country are investigating their own types of valves in dogs but to my knowledge, none of them are yet quite satisfactory. In the meantime, until we get a satisfactory replacement for the diseased aortic valve, it would appear that aortic stenosis is operable in some cases and that aortic insufficiency is probably still inoperable.

The commonly employed operations for aortic stenosis have been trans-ventricular dilatations with the instrument devised by Bailey and his co-workers, or more recently the trans-aortic blind approach devised by Swann and independently by Bailey. In using these operations the surgeon is faced with two important difficulties. The first is that the valve is badly diseased and difficult to work with and the second is that the approach is blind. Since he does not see the valve he frequently will split only one of the three commissures or he may split one commissure and tear a valve cusp inadvertently and thereby produce insufficiency. I think the blind approach is far less suitable for the aortic valve than it is for the mitral valve. One advantage of the blind approach, with the finger in the atrium for the mitral valve, is that you can gauge the degree of insufficiency which occurs when you dilate the valve but this is impossible in the aortic valve because you cannot put your finger through the left ventricle wall. If you put your finger in from above, it is on the wrong side of the valve in order to gauge the insufficiency you may be producing.

I think, even at the present time, probably the best way to treat

aortic stenosis is with an open operation and we have used such an operation, employing hypothermia. I should speak cautiously as we have used it on only four patients, but a number of people around the country are interested in similar approaches to the aortic valve. I feel there is more justification for an open approach on the aortic valve than there is on the mitral valve at the present time, though it will never achieve the kind of mechanical result you want until the diseased valve can be completely replaced.

MODERATOR EICHNA: *What did you do in those four patients, Dr. Lewis?*

DR. LEWIS: We occluded the cardiac inflow after the body temperature had been lowered and also occluded the aorta distally just beyond the ascending aorta. Both pulmonary roots had also been occluded. An incision was made in the ascending aorta and by just opening that incision you could look right down on the aortic valve from above and cut the three commissures open, out to the aortic wall, carefully, under direct vision.

MODERATOR EICHNA: *What do you do with all the calcium you find?*

DR. LEWIS: Nothing, just leave it there.

MODERATOR EICHNA: *Can you cut through it?*

DR. LEWIS: You can cut through it with a heavy knife or scissors. Your first inclination would be to take your time and peel the calcium out of the valve cusps. If you study one of these badly diseased valves you quickly find that this is unwise because when you peel calcium out of the valve the valve is destroyed. I don't think you can peel the calcium out. I don't think you can sit and take your time and reconstruct a good aortic valve out of a badly stenosed and calcified one.

MODERATOR EICHNA: *What kind of result did you get?*

DR. LEWIS: There were four patients. One was an operative death. Three are living. One is a result that I think anyone would agree was an excellent result and the other two are improved but it so hard to prove this, as it is difficult to get objective information on aortic stenosis patients, as you all know.

I believe the technique of left heart catheterization to determine differential pressures across the aortic valve should be helpful but I have had very little experience with it and I would like to hear the opinion of those who know more about that subject. It seems like the best way of trying to evaluate critically the surgery of this valve and it should

be the best way of trying to differentiate insufficiency from stenosis, which is crucial in this disease.

MODERATOR EICHNA: *Yes, Dr. Glenn?*

DR. GLENN: First, I think Dr. Lewis is too modest. If I am not mistaken, he is the one who really proposed this open procedure. I have two slides that I would like to show to emphasize what he said. The indirect approach that has been mentioned is the one that is being currently used.

(Slide) This is just the valve to show the amount of calcification. One of the difficulties in this indirect procedure is that when you put a valvulotome through and break it up you may break off a piece of calcium and have it lodge right in the orifice of the coronary and have a death on the table.

(Slide) This is the open procedure which I think is the procedure that we should expect to use in the future. This is an opening. This is Dr. Lewis' operation which he has already described to you. This gives the advantage of being able to see what you can do and of staying away from the coronary orifice by following the fissure.

(Slide) The other slide shows the indirect procedure. Here is the valvulotome which is inserted through the wall of the ventricle and into the aortic valve and then opened. If a split results, that is good. If it doesn't, it may be you pushed on through and then the operator may indulge in the very crude maneuver of dragging it back. This is certainly fraught with danger. Nevertheless, I think in aortic stenosis it may be done. I also think that before any operative procedure is undertaken,—that is on the valve itself, one should take pressures in the aorta and also in the left ventricle and then proceed with the operative procedure. I believe this should be done afterwards also. Unfortunately there are too few surgeons reporting their results. I believe there will be more reports within the next year because there are a number of people who have accumulated some experience such as ours. With this we have not used the open method that Dr. Lewis and Dr. Swann have described.

Dr. William Glenn at Yale has been sewing a diverticulum onto the aorta at the site of the opening. By inserting a finger and guiding the scissors with the finger there is less likelihood of damage to the coronary orifices. I am reluctant to sew a diverticulum onto the aorta, however, because if it happens to be calcified there may be some difficulty in

getting it together. It may also be the site of an aneurysm later.

MODERATOR EICHNA: *Is there any further comment, Dr. Lewis?*

DR. LEWIS: No.

MODERATOR EICHNA: *I should like to ask what happens to the coronary flow during this time? Dr. Glenn did mention the possibility of embolization with a piece of calcium. What about air embolism?*

DR. LEWIS: Air embolus can be prevented. We studied that quite extensively in animals. Air embolism is a real hazard in the left heart open operations, without any question. In dogs 0.5 cc. of air per kilogram in the left atrium is almost uniformly fatal. Some can be resuscitated but most succumb. Strangely enough, far more air can be tolerated in the ascending aorta of the dog than in the left atrium, which is reassuring but by practicing a careful technique of washing the air out before closing the aortotomy, air embolism can be avoided and it has been in our dogs and in our human experience so far. We spend a good deal of our time getting the air out. We release both cavae, both pulmonary roots, inject saline under pressure into the left atrium and inject saline under pressure down through a tube passing into the left ventricle through the aortic valve. We have a clamp in position on the aorta to close the aortotomy and when several big heart beats full of saline and blood finally come rushing out to flood the field, we finally clamp the aortic wound and release the distal clamp. It is a little tricky. One of the hazards that one might think would occur, but does not, is for air to get into the coronary arteries while the aorta is open and the coronary orifices exposed. Air does not get into the coronary arteries at that time. Henry Swann of Denver has demonstrated this particularly well. There is no air embolism as coronary flow does not occur during this time with this particular method.

Walter Lillehei and Dick Varco have used a method developed by Adam and his associates in Puerto Rico, in which the coronary system is perfused in a retrograde fashion by perfusing through the coronary sinus. The right atrium is opened and a cannula is placed in the coronary sinus to perfuse the heart at the time that the rest of the circulation is perfused with a pump-oxygenator. Whether this is necessary or not, or desirable, or fraught with too many hazards of its own I don't know. Nor do I believe we can say at the present time. I think it is an important question. Our human experience is small, but I have the distinct impression that many of these people have coronary insuffi-

ciency to begin with due to some calcification in their coronary arteries, and some method to perfuse the coronaries during this time would doubtless be desirable.

MODERATOR EICHNA: I don't think one can quarrel with that wish. *For how long a period is the aorta exposed, Dr. Lewis?*

DR. LEWIS: In our hands it is only about four to five minutes, but it could be a little longer, I imagine.

MODERATOR EICHNA: *With cardiac contraction persisting, I don't see why air does not get into the coronary artery. Dr. Cournand, do you have an explanation for that?*

DR. COURNAND: No, but I am not familiar with the exact situation. May I make some comments with regard to surgery in aortic stenosis? In those cases which are quite easy to diagnose the results of surgery are not good. In addition to the reduction of the stenosis there is the complication of liberating calcium. Development of an aortic insufficiency is not unusual. Incidentally, in the case with a satisfactory result, has the patient developed aortic insufficiency of any significance?

DR. LEWIS: No.

DR. COURNAND: This is probably the very rare instance. With regard to the problem of maintaining coronary circulation, I have no information at all. Probably this will be the type of surgery which will best be done with cardiac arrest rather than with hypothermia.

DR. LEWIS: The problem there would be to restart the heart, because you are not perfusing the heart. If you are not perfusing the coronaries and have the heart in arrest, then you would have to restart the heart by washing out the prostigmine or potassium and you would have to perfuse the coronaries before you could do that. It is a tricky little problem.

MODERATOR EICHNA: *There are now a number of questions which have been submitted by the audience. I would like to try to obtain answers to some of these. Let us go back to air embolism. Dr. Dennis, I understand you have some observations on that problem.*

DR. DENNIS: I am but one of many I suspect, Dr. Eichna. The question of air embolism arose because of the interest of my associates and me in artificial heart-lung machines. We found that we were unsuccessful in an early series of perfusions in animals and had no good explanation for it. Ultimately it dawned on one of us that air embolism was the probable explanation. Therefore we set out to try to evaluate the prob-

lem of air embolism directly. We injected air into the carotid on one side in the dog using, in some instances oxygen, in some instances air, in some instances rapid injections and in some instances slow injections. The interesting thing is that air injected in this fashion is lethal at a given amount per kilogram which runs around 1.5 cc. per kg. regardless of the rate at which it is injected. It is just as frequently lethal if it is injected in minute amounts or bubbles over a period of half an hour. This danger also exists if one large injection is given in rather abrupt fashion. The problem is a very real one. We found that when the air was injected very slowly in these animals, they would develop somewhat deeper anesthesia, a slight rise in blood pressure, not much change in pulse, that neurological changes were seldom striking, but the dogs would wake up more slowly afterwards and be somewhat somnolent. They would get up, walk around the room, frequently eat food if it were offered to them, then the animals would become drowsy in a period of some hours following the injection. We found that the blood pressure at this time was down and that the animals would die in approximately 12 to 24 hours after the injection of air. This is a matter of some importance because of the current enthusiasm in this country for the use of bubble-type oxygenators for the purpose of carrying the circulation during open heart procedures.

I know of two centers in which surgery has been performed using bubble-type oxygenators where patients with the same clinical picture which I have described in our dogs have been lost. If one does not specifically look for the air embolism and know exactly what to look for, from a pathological point of view, it is unlikely that air embolism will be suspected.

We have seen animals killed even though air was injected so slowly that careful autopsy could not detect any bubbles of air in the minute vessels in the pia mater over the brain.

I have one slide that I would like to show. (Slide) This is a section of the cortex of a dog that received an injection in the way that I have described. This dog recovered. He had some neurological deficit which gradually diminished and almost disappeared within a few weeks following the experiment. The dog had only slight difficulty with balance at the time he was sacrificed and yet a section of the brain shows a large area of cortical degeneration. We have found that it is difficult to recognize this lesion shortly after such injection. However, if fluorescein

is injected just before sacrificing the animal and a photograph of the brain made with ultraviolet light, it becomes apparent that central areas on the lateral cortex on either side will fail to fluoresce and we can assume that this is the area which has suffered most and in which the greatest amount of degeneration will occur later on. Therefore, even though these people may apparently get well, to the extent that they are discharged from the hospital and return home, their condition must be regarded with great suspicion and the possibility of serious damage is potentially great.

MODERATOR EICHNA: *I think that we have now touched upon another major problem in the surgical management of heart disease which indicates that certain techniques are necessary for the management of various types of operations. We might now consider some of these newer techniques and I shall ask Dr. Dennis to discuss the problem of extracorporeal circulations.*

DR. DENNIS: I should first point out that the idea of utilizing an apparatus capable of performing the work of the heart and lungs is the idea of Dr. John Gibbon of Philadelphia. He worked on this long before anyone else became interested in it as a clinical possibility, and fittingly, several years ago Dr. Gibbon was the first man successfully to use such an apparatus in complete closure of a septal defect.

My associates and I did not attempt this operation until Dr. Gibbon had worked on it for almost 15 years. This was in 1947. I can quickly describe for you some of the difficulties that we have had and go over the difficulties that confront anybody who tries to use an apparatus such as this.

In the first place, one might well question, why replace the lungs as well as the heart with such an apparatus? It is simply a matter of the complication of the incannulating technique. There are so many cannulas and tubes involved and so many incisions to be made in vessels in attempting to shunt around the heart, but not the lungs, that it has failed as a practical procedure. There are many ways of getting an adequate exchange of oxygen and CO_2. The bubble oxygenator devised by Dr. DeWall at the clinic of the University of Minnesota, is one that is very satisfactory in his hands, and with which he eliminates the risk of bubbles in his patients. There are other techniques. The most beautiful is that of Dr. Gibbon in Philadelphia in which a stationary screen is used to film the blood for purposes of exchange. I will show you in

a moment the one we use. The type of pump used is very important. One should use a pump which will result in a minimum of hemolysis and one which will be automatically controlled so that one does not pump all the blood out of the oxygenating reservoirs and produce in the patient an embolus of oxygen from the oxygenating atmosphere. This happened to a patient whom we were perfusing in 1951, and it was of course a fatal error.

Another problem encountered is the clotting mechanism, but I believe that most medical centers have succeeded in adding enough heparin to prevent clotting in the machine and yet little enough heparin to avoid failure of hemostasis at the end of the procedure.

The problem of hemolysis is a complicated one. The flows must be streamlined, and many problems are surmountable. I have already said something about gas embolism which about summarizes the major problems.

With the help of a motion picture I can show you what our particular apparatus looks like. (Motion picture) It is not the only one. I am not sure it is the best one. This is the machine which oxygenates. We have tried to follow techniques learned from the food processing industry so that this apparatus comes apart completely and can readily be cleaned. The essential part of the oxygenator is the steel screen disc of which there are four in this unit, rotating approximately 24 times a minute. The purpose of the rotation is to permit spontaneous filming, whereas in Gibbon's apparatus, filming becomes a very complicated problem with stationary screens. If he loses the film during perfusion because the flow stops momentarily, he is then unable to reconstitute the film. The jets lay blood in a film on the center of the screen in an oxygen atmosphere. Some use CO_2 as well as oxygen. We are willing to settle for cutting the partial pressure of CO_2 in half during perfusion and this seems to avoid any real problem.

This is the arrangement of the jets and screen. The apparatus is placed upon the floor so that we will use only one blood pump and have to pump blood only once. In other words, we siphon blood out of the vena cava and pump it back through the left subclavian artery into the arch of the aorta. This is the apparatus with the pumps in front. These particular pumps have a diaphragm below which are contact points which activate the solenoid valves which, in turn, govern the flow of compressed air so that the pump never empties unless gravity flow fills

it from above. It simply stops, and air embolism from the reservoir cannot occur.

This is our combined filter and bubble remover. Although we believe that we don't get any bubbles at the present time we are nevertheless so sensitized to bubbles that we have a bubble remover in the circuit. This is an ordinary stainless steel scouring pad from the Diamond K Store; it has been treated with silicone or antifoam and it works very satisfactorily indeed.

This is the arrangement of the pumps. We are not yet as elegant as we could be and they are set on the floor. Priming is simple and achieved by making a shunt from the arterial tube to the venous tube for a short period of time and pumping until the transparent tube indicates that no residual gas bubbles are in the circuit.

The manner in which the pumps work can be seen here. The pump shown has a 75 cc. stroke output. The two pumps work alternately producing a fairly smooth stream of blood. Several hundred animals have been perfused satisfactorily with this apparatus up to the present time. Only nine patients have been perfused with this apparatus to date but so far we are very gratified with the performance of the apparatus. I am embarrassed to be the one discussing this. My former associate and Dr. Lewis' former associates, Dr. Lillehei and Dr. Varco, should be the ones discussing this because they of course were the first ones to use an oxygenator in a large series of patients.

MODERATOR EICHNA: *Dr. Lewis, have you any comment on this point?*

DR. LEWIS: We have all been interested in Dr. Dennis' work in this field for many years. If he wasn't the first one to start using pump oxygenators, I imagine he was the second after Dr. Gibbon. I think he made the first clinical trial of this apparatus in man. Anybody dealing with heart surgery is deeply concerned with pump oxygenators and those who have less experience than Dr. Dennis are perpetually concerned with what type of oxygenator to build next. Stimulated by Dr. Gleidman, who came from Dr. Dennis' school and worked in Minnesota for a while, we used bubble oxygenators for some time and now I am interested in the possibility of working with membrane type oxygenators. What do you think of those as a possible type of oxygenator, Dr. Dennis?

DR. DENNIS: I think there are several of them that are very promising

indeed. The one that Dr. George Clowes has recently developed in Cleveland is particularly promising. It is a rather compact and ingenious unit. Provided the membrane remains intact, no gas gets into contact with the blood.

DR. LEWIS: You tried membranes many years ago.

DR. DENNIS: It is the old story. I had the membrane but did not show the ingenuity that Dr. Clowes has shown.

DR. LEWIS: We have used hypothermia in doing many open heart operations but I suppose most authorities believe that hypothermia is a sort of stop-gap method of doing open heart surgery. It is difficult for me to predict whether the method has any future but it does work and with a relatively small amount of machinery. It is probably the simplest method mechanically of doing open heart surgery, though it is, as you might expect, quite complex physiologically. It is based on the simple principle that when a patient's body temperature is lowered his oxygen requirements go down, provided that he does not shiver, and by lowering the body temperature to between 85° and 90° F. it is possible to occlude the entire inflow to the heart for a period which is indeterminate in humans, but seems to be about 15 minutes in the dog. In humans, perhaps less than eight or nine minutes would be the safe period.

Certainly by a carefully schooled technique a number of intracardiac defects can be repaired in that period of time but lack of time is the most serious defect with hypothermia. As a method of doing open heart operations this time deficiency with hypothermia can be overcome, at least partially, by adding coronary perfusion for certain types of operations and perhaps by using a small heart-lung machine, or by lower rates of perfusion. It is intriguing to think that by lowering the body temperature to some degree you might be successful with a smaller oxygenator. I should like to hear Dr. Dennis' reaction to that.

However, I do want to point out, that for somebody like myself who works with hypothermia, shifting to a pump oxygenator is a complex procedure because the team that runs it must be well trained and used to running the machine. The problem of heparinization also arises. Postoperative bleeding is of some concern and special blood donors must be available to use in conjunction with the procedure since the machine has a fair volume capacity that has to be filled with specially cross-matched blood. It is these complexities that make it inadvisable to adopt such a machine for general use at the present time.

MODERATOR EICHNA: *From the physiological standpoint, Dr. Cournand, what is your opinion about the problems to the patient of the pump-oxygenator procedures? I agree that these devices are ingenious. I agree that they often act as satisfactory shunts. I sometimes wonder if the physiological status of the patient is kept in mind sufficiently. What are the problems that he faces?*

DR. COURNAND: I believe there are now a sufficient number of satisfactory results to indicate that the extracorporeal circulation with the pump-oxygenator is an excellent method. Furthermore, I am under the impression that those who are in favor of hypothermia are losing ground. Dr. Lewis did make a remark which is quite important, namely that at some time if it has not already been done, both procedures might be associated. There is no doubt that hypothermia has demonstrated quite remarkable results.

While I was in Europe I met Dr. Brom of Leyden, who has operated upon 79 cases of interatrial septal defect and the last 30 without a single operative death, certainly quite a miraculous result.

When it comes to the repair of intraventricular defects, which take longer to repair, then the problem will become much more serious. I was impressed by what I have seen when extracorporeal circulation was employed but it is quite important that those who use it should be aware of the possibility of cerebral damage.

I don't have very much more to say on this subject, not having studied it personally. During my visits to a number of laboratories where extracorporeal circulation is carried out, particularly in Paris at the Hospital Marie-Launelongue, I was quite impressed by the quality of the work which requires such perfect team work.

MODERATOR EICHNA: *The questions that come to mind are the amount of flow that is required, the problem of CO_2 and the problem of temperature. Dr. Dennis?*

DR. DENNIS: The flows have been widely estimated. When Dr. Varco and I and our associates operated on two patients in 1951, we were under the impression that the flows should be very high, and the first patient in whom the old apparatus was employed had blood perfused through him at the rate of 220 ml. per kg. per minute, which is I suspect, approximately twice what the normal blood flow would have been for such a subject.

More recently, Andresen, in England, pointed out what is referred

to as the azygous flow principle, namely, the amount of blood which returns to the heart through the azygous vein is enough to sustain a dog over a period of a half hour if the cavae are temporarily occluded. Drs. Lillehei and Morley Cohen accepted this after study and put it in clinical use in the cross-transfusion experiments that they and Varco did together, which of course electrified everybody else who was thinking about working in this field. They used flows of around 30 ml. per kg. per minute, and this worked very satisfactorily. The best results, as far as I know at the present time, are being obtained by Dr. Kirklin and Dr. Wood and their associates at the Mayo Clinic, who are using a very slight modification of Dr. Gibbon's machine. They are maintaining flows somewhat higher than this, I believe around 65 ml. per kg. per minute, and doing very detailed studies of physiological and biochemical changes in the course of the perfusion. In the hands of their marvelously coordinated team this method maintains a very appropriate level of the blood constituents and physiological observations as far as relation to normalcy is concerned.

DR. COURNAND: Satisfactory is a term I don't like to use. It seems to me that the flow of 30 ml. per kg. corresponds to about 2100 ml. for an average size man or two liters per minute, just two liters. I have seen people who could be revived after a period of time during which their flow, as the result of shock, for example, was reduced to something like one liter per square meter, which is approximately of the order of two liters in all. Undoubtedly, if you use a pump that can deliver two liters, there is no fundamental physiological damage which will accrue from that, providing that it is not too prolonged.

MODERATOR EICHNA: It appears that this is the reason why the surgeons who have dealt with congenital heart disease in children have found the pump so effective. Children do not require as large a flow as an adult.

DR. DENNIS: The pump with the two liter output does appear, as Dr. Cournand says, to be adequate for adults but it is only by virtue of the combination, as far as our group is concerned, with a drop in body temperature. We have deliberately dropped the body temperature to 91° F. believing this could be done without getting into trouble with the various conduction difficulties which bother all of us who try refrigeration, except Dr. Lewis. Is that not right, Dr. Lewis?

DR. LEWIS: They may not bother me but we have difficulties too.

Conduction difficulties at lower temperatures are very common and may or may not be serious. I don't think they are usually serious.

DR. COURNAND: Are they any more serious if the patient has been shivering? Can you avoid shivering?

DR. LEWIS: You can avoid the shivering but I don't know definitely how to avoid some conduction disturbances. If you get an animal cold enough, some type of heart block is almost unavoidable. The fact is the animals that we have cooled to the lowest temperatures with survival, that is, temperatures just a few degrees above freezing, have all had cardiac standstill but don't go into standstill suddenly. They go through a period of complete heart block and finally cardiac standstill. If they don't have the standstill, they don't survive the deep cooling experiment. Standstill is important in that particular experiment.

DR. COURNAND: Isn't it quite remarkable, Mr. Chairman, that as a result of the progress of cardiac surgery the surgeons are sometimes able to speak with a little more authority about the physiological problem than those who profess to be physiologists?

MODERATOR EICHNA: *I believe we have time for one more aspect of this discussion, that is, we are now face to face with the problems of cardiac standstill surgery. Who on the panel would like to start that discussion?*

DR. DENNIS: I don't think anybody is trying to use standstill surgery in the absence of heart-lung machines. It would not seem very safe, would it? We have not used standstill clinically, as yet at least, but have used deliberate electrical ventricular fibrillation. The reason for this being that, if one makes a large opening in the ventricular septum or if one opens the left side of the heart, air is likely to be aspirated into the left side of the heart and ejected into the aorta at the next contraction, provided the heart is beating vigorously while this procedure is going on. Ventricular fibrillation appeared to us to be a way to avoid this problem. For instance, in cutting out the mitral valve in our dogs and putting the prosthetic mitral valve in place, we found that we had about 80 per cent mortality if we endeavored to do it without ventricular fibrillation, whereas the mortality was about 20 per cent if we did it with ventricular fibrillation. The utilization of various agents, acetyl choline or potassium chloride, for the purpose of acquiring a completely flaccid heart, is something that we have started to investigate so recently that I don't feel competent to say a great deal about it.

DR. LEWIS: I disagree with Dr. Dennis on a couple of points. Cardiac arrest, of one type or another, has been used electively with hypothermia as well as with the heart-lung machines. We used ventricular fibrillation experimentally some time ago, with hypothermia to overcome the same problem he mentioned in operating on the left side of the heart. Furthermore, Moulder of Chicago and Conrad Lam of Detroit have both used prostigmine in order to obtain standstill with hypothermia. The potassium standstill or the prostigmine standstill might work fairly well with hypothermia and in a coronary perfusing technique. I hesitate to go any further because of lack of experience.

MODERATOR EICHNA: *Dr. Glenn, have you any comments on these points?*

DR. GLENN: I have had experience with the heart-lung-pump and cardiac standstill only in the laboratory. I have been much interested in the clinical work that has been done. It seems to me that the present trends will result in a machine that will be utilized with considerable safety in that it will take over the two functions of the machines. Then with cardiac arrest probably induced with drugs, we can work upon the heart.

What part hypothermia will play here I don't know. Certainly hypothermia is a great boon at the present time to those of us who cannot successfully utilize a heart-lung machine, and therefore I think we, who are in that category, should continue to use it until the other has been improved more.

The one great need in this country at the present time in regard to the heart-lung machine is that, in addition to the careful studies such as are being done by Kirklin and his group, there should be an accumulation of a large number of studies of clinical cases including those not successful. Those of us who are trying to learn these new techniques and are stubbing our toes need more specific data. I furthermore think it should not be embarked upon lightly. Anyone who uses these machines should be well grounded in the work of the experimental laboratory before moving into the operating room.

MODERATOR EICHNA: The course which the panel has taken has *not* been that which the Moderator had originally planned for the meeting. I think panels are a bit like sorcerers' apprentices. They get out of hand and then they run their own courses. In this instance the course the panel has taken could not have been better because I think you will

appreciate that for the last two-thirds of the time we have been discussing the newer methods of performing cardiac surgery, not so much the choice of patients, not so much the results but taking a look into the future, considering what the surgeons are trying to do, the type of equipment they need, the condition in which they would like to have the heart. We have left untouched the problem of congenital heart disease, and thinking about that, it occurred to us that the problems in congenital heart disease today are those of the cardiac septal defects. Their correction requires development of special apparatus, methods and techniques.

I think the panelists would perhaps agree that any sound approach to these pressing problems of cardiac surgery would be the solving of those problems which involve the pump-oxygenator, hypothermia, cardiac standstill surgery and cardiac fibrillation surgery. Is this a fair statement, gentlemen?

This leads to the final question which is, what would you recommend to the physician who has under his care today a patient with an interatrial septal defect, or interventricular septal defect, or a cardiac malformation which presents several complications? Should that patient be operated upon today or should he await the development of newer and better techniques than those which have been discussed? How do you feel about that, Dr. Cournand?

DR. COURNAND: With regard to atrial septal defect, only one question arises, i.e., whether those who are asymptomatic and with normal arterial pulmonary pressure should be operated upon or not. Dr. Brock, leading a round table conference recently in Stockholm, was of the opinion that they should all be operated upon and probably at a relatively young age for technical reasons. This was not the opinion of all the panelists, including two surgeons, although Dr. Brock in summarizing, conveyed the impression that it was the opinion of everybody. I think the question is still open. I am not in a position to take a definite stand. If at some time in the future the surgical risk is negligible, then one might possibly conceive that asymptomatic and uncomplicated types of atrial septal defects should be operated upon.

With regard to the interventricular septal defect, there are only two institutions in this country, where I would send a child for corrective surgery, provided that pulmonary hypertension is present. That about sums up my reaction.

MODERATOR EICHNA: *Dr. Lewis, would you like to comment on this problem?*

DR. LEWIS: I have recommended surgery for all symptomatic patients with atrial septal defects. I have recommended it less emphatically in some than others. Those who have very few symptoms and have low pulmonary artery pressure, don't need surgery as urgently as those who are growing a little older and have high pulmonary artery pressures. Most patients with this defect come to you at an age between 15 and 30, and once they are over 25 I have recommended surgery more urgently. Also, I believe the disease is gradually progressive. The mortality rate of the operation for the foramen ovale defects is probably as low as it is apt to get. In the last 18 or 20 operations we have done there have been no deaths. Any heart operation will always carry some risk. If you can differentiate the persistent ostium primum type of defect, I would be more cautious about recommending surgery for that one.

DR. COURNAND: Would you recommend surgery in those cases in which the valves are involved? Apparently the results are pretty bad.

DR. LEWIS: It is very hard to tell that ahead of time. Unfortunately, I must say our poor results among the survivors have fallen into two groups; those with persistent ostium primum defects, who are apt to get complete atrioventricular heart block and those with mitral disease, which in my experience usually turns out to be insufficiency.

We have done only five patients with atrial septal defects and mitral stenosis. Two are worse than they were preoperatively. The others are all right. If I had a patient who I felt quite sure had stenosis of the mitral valve and not insufficiency I would recommend surgery. This problem is a little unsettled, I think.

MODERATOR EICHNA: *Dr. Glenn, what is your opinion on this problem of operation for septal defects today?*

DR. GLENN: In the first place, there are only a few clinics in the country today that are doing this with a mortality range that I feel justifies surgery. Things are changing rapidly. Great progress is being made. I should say in selecting the place to send your patient, be open minded in selecting those institutions which are beginning to take patients for an operation in which the outlook is grave. Five years from now will see this on a great deal firmer basis. Furthermore I want to speak a word of caution about believing that once a diagnosis is made it is an indication for operation. We are in a learning phase, careful consideration and

wisdom are needed in selection of patients for operation. Prognosis without operation must be balanced with the risk.

DR. DENNIS: I certainly echo what Dr. Glenn has said. As far as the interventricular septal defects are concerned, I don't speak from personal experience because I have had too little of it. But the experience that Dr. Varco and Dr. Lillehei have had would suggest that the patient who is suffering from a mounting pulmonary artery pressure, with interventricular septal defect is a patient who should have the defect closed. When the pulmonary artery pressure is 70 per cent of the systemic pressure or higher, the risk is very great, whereas, if it is lower than that, it is a great deal better. I think their opinion in this matter is, but I am not sure, that the patient with an asymptomatic ventricular septal defect is not a candidate for operation. That is the policy we are following. At least the patient must be symptomatic and seriously symptomatic or operation is not considered.

MODERATOR EICHNA: Dr. Cournand has indicated that it is not necessarily the function of a Moderator to summarize the consensus of the panel, but I am going to overstep that caution for the moment. Could we say gentlemen, that today the status of surgery for heart disease is such that, in view of the rapid development of techniques, which seems to have a solution in the foreseeable future, it would be well worth while to exercise considerable caution and withhold operation, both for acquired and congenital heart disease, in those patients who are asymptomatic and whose cardiovascular physiological measurements are not particularly abnormal; whereas in those individuals who are symptomatic or whose cardiovascular physiological measurements are distinctly abnormal and indicate that their probable life expectancy may be shorter than the duration of time necessary for development of improved techniques, in these patients the now considerable risks of operation should be taken? May that be considered as a consensus?

DR. GLENN: Yes.

MODERATOR EICHNA: I think this will close the panel meeting. Thank you all.

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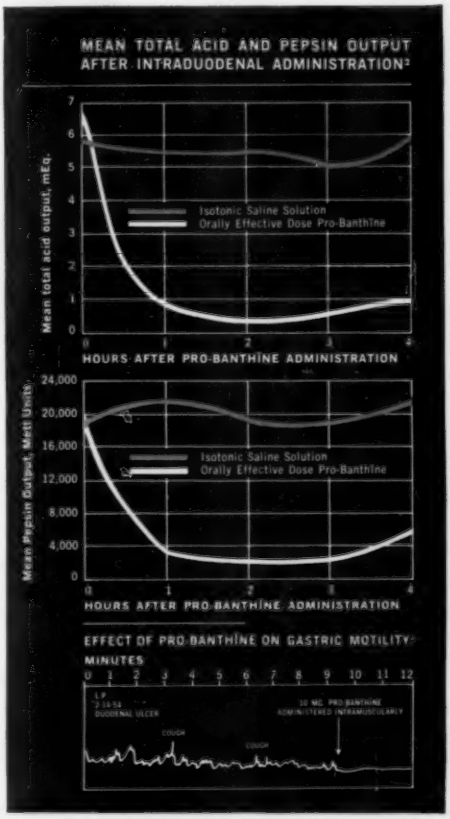

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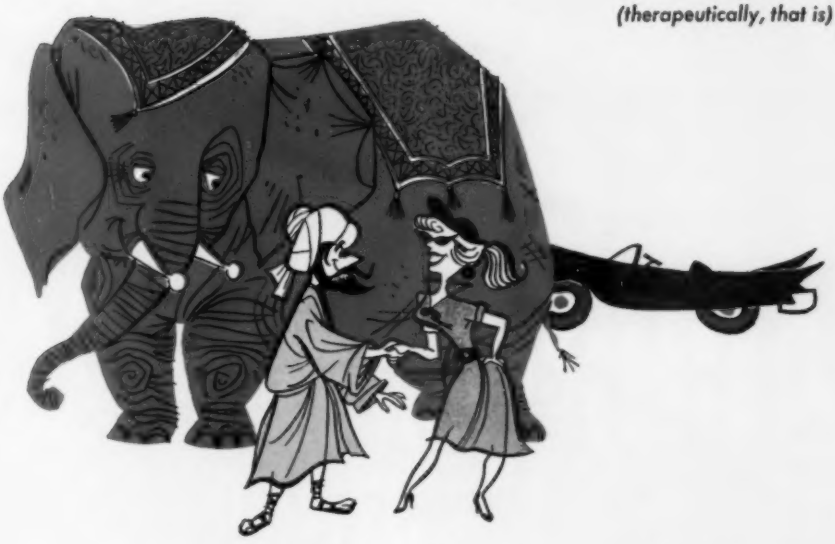

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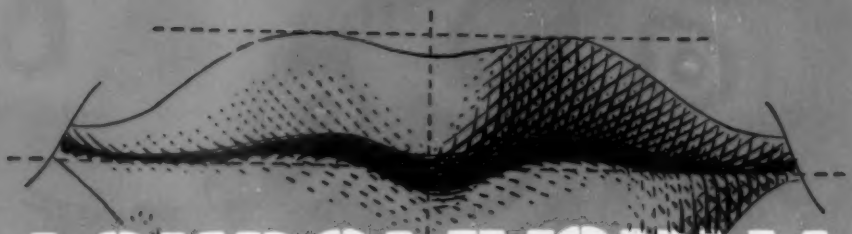

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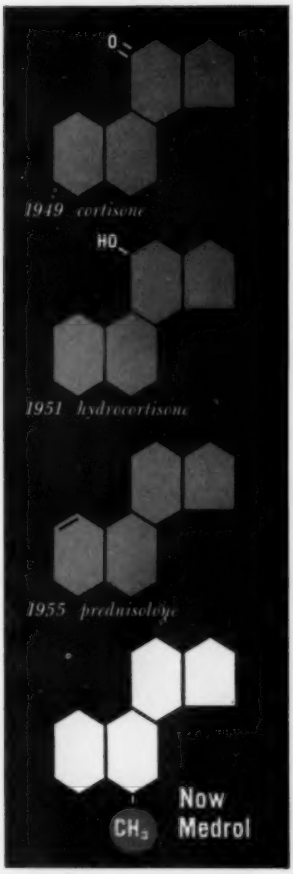

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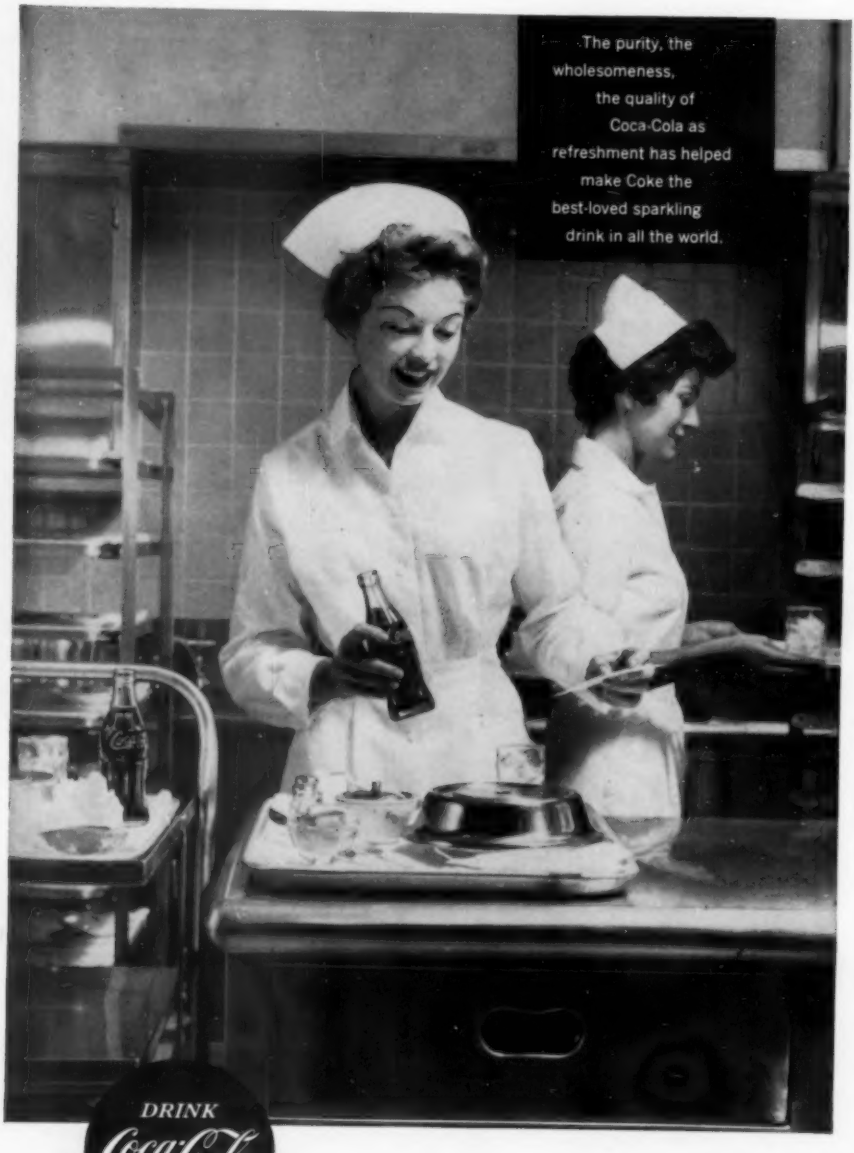
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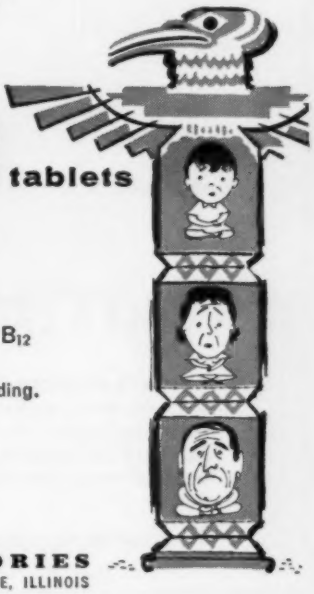

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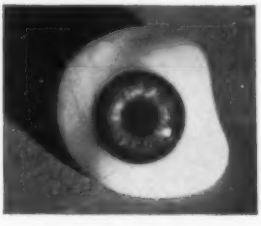

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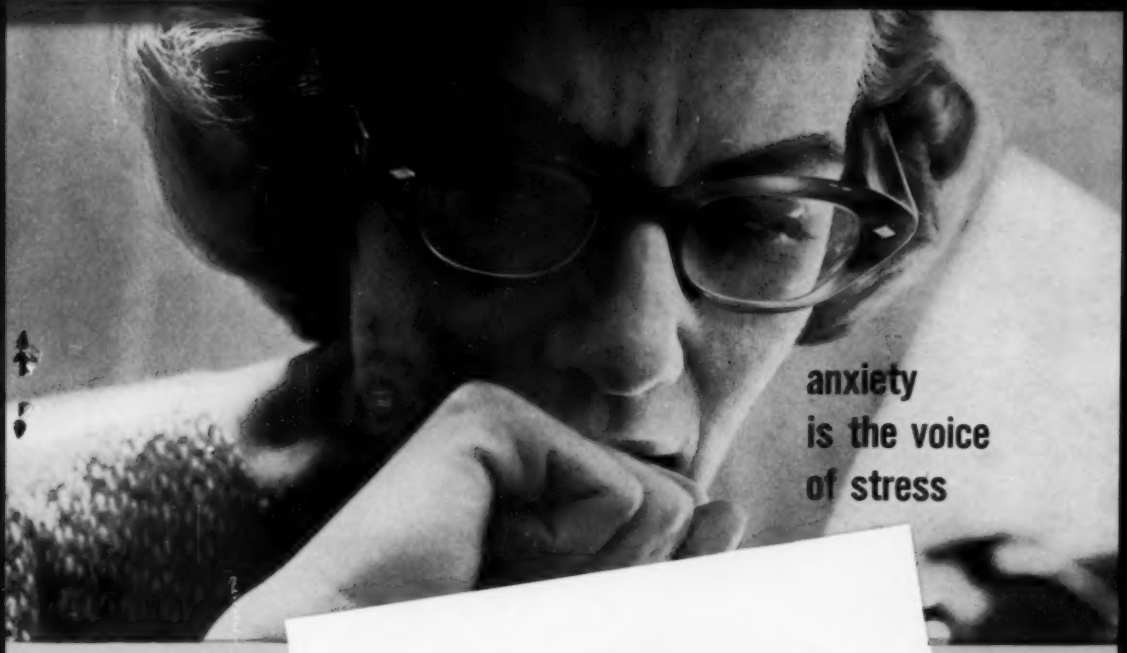

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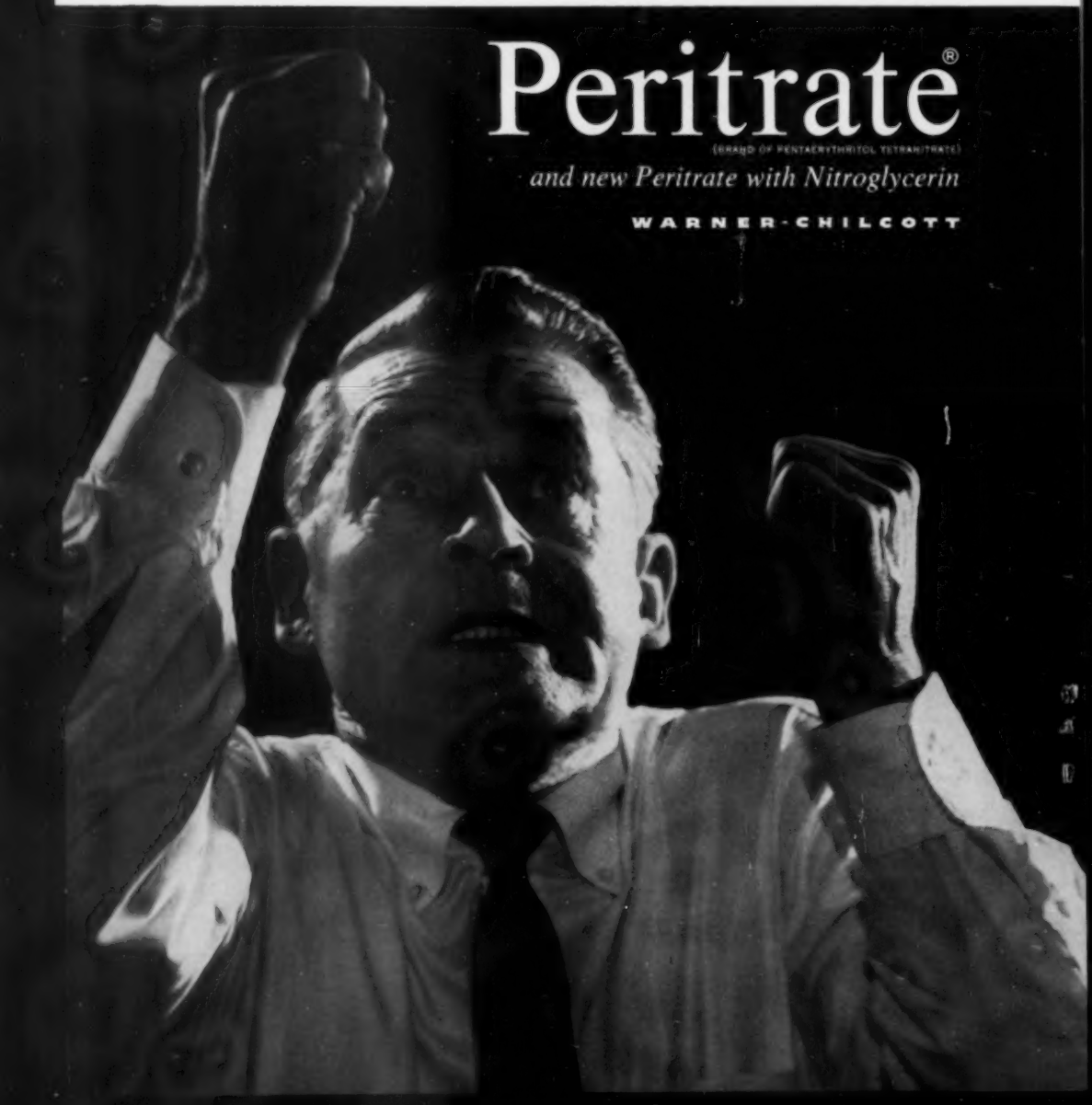

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